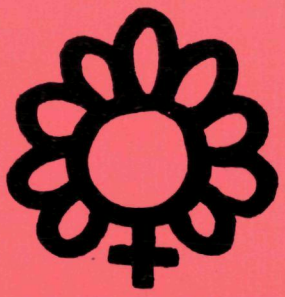
# SCREENING FOR CERVICAL CANCER

## THE NIJMEGEN PROJECT



YOLANDA VAN DER GRAAF

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## THE NIJMEGEN PROJECT

This study was part of the long-term Research Programme "Quantitative microscopy, cellbiology and epidemiology of (pre)malignant lesions"

# SCREENING FOR CERVICAL CANCER

## THE NIJMEGEN PROJECT

PROEFSCHRIFT

ter verkrijging van de graad van
doctor in de geneeskunde
aan de Katholieke Universiteit te Nijmegen,
op gezag van de Rector Magnificus Prof.dr. B M.F. van Iersel
volgens besluit van het College van Decanen
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door

YOLANDA VAN DER GRAAF

geboren te Roermond

Promotor : Prof.dr. G.P. Vooijs
Co-referent : Dr.ir. G.A. Zielhuis

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## *INTRODUCTION*

In The Netherlands about 300 deaths per year are due to cervical cancer and about 1200 new cases of invasive cervical cancer are diagnosed every year (1-2) The incidence of cervical cancer in The Netherlands is comparable with the incidence in other Western countries and relatively low compared with the incidence in parts of Latin America (3)

The etiology of cervical cancer was subject of numerous studies Like other cancer types, the risk of cervical cancer increases with age Women with an early age at first sexual intercourse and women with a history of multiple sexual partners are more likely to develop cervical neoplasia (4-8) Also the sexual behaviour of the male partner seems important and indicates the infectious and venereal transmission of cervical cancer (9) Human papillomavirus, a sexually transmitted agent, is increasingly implicated in the pathogenesis of cervical cancer (10) Recently it is suggested that cigarette smoking plays a part in one of the earlier stages of cervical carcinogenesis (11) Nicotine and cotinine can be detected in the uterine cervix of cigarette smokers and could possibly have a genotoxic effect on the cervical epithelium (12)

It is self-evident that primary prevention of cervical cancer on basis of this information is practically impossible Therefore early-detection programmes have been developed George Papanicolaou (1883-1962)

proved the usefulness of exfoliative cytology in the diagnosis of early uterine cancer. He performed his studies between 1925 and 1943 and gradually the "Paptest" was adopted on a worldwide basis. After promising results of cervical screening in other countries, in The Netherlands population screening was introduced in 1976 in three pilot regions (13-16).

This thesis deals with several aspects of the evaluation of one of the three pilot programmes i.e. the one in Nijmegen region. In order to be able to interpret the change in mortality after introduction of the screening programme trends in cervical cancer rates in The Netherlands for the past five decades are described in Chapter 1. To estimate the effect of changes in therapy in the last 15 years on mortality figures a survival analysis was performed. Survival rates of women with invasive cervical cancer in the period 1970-1985 are presented in Chapter 2.

Chapter 3 gives a description of the cervical screening programme in the region of Nijmegen. In this chapter a summary is given of the organisation of the screening programme and of attendance, referral and detection rates.

The main aspect in the evaluation is the effectiveness of population screening for cervical cancer. The effectiveness of the Nijmegen programme was studied in two ways. In Chapter 4A the results of a population-based case-control study are described. In this study, participation in a screening programme was reviewed as a preventive factor for invasive cancer.

The effectiveness of the screening programme was also evaluated by determining changes in the incidence rate of invasive cancer of the uterine cervix (Chapter 4B).

An important aspect of the effectiveness of a screening programme is the validity of the screening test which is discussed in Chapter 5.

Chapter 5A deals with the false negative rate in cervical cytology and Chapter 5B with screening errors.

In Chapter 6 all aspects of screening are briefly reviewed in the light of public health policy.

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*CHAPTER 1*

# *CERVICAL CANCER MORTALITY IN THE NETHERLANDS**

Yolanda van der Graaf MD, Gerhard A Zielhuis MSc, PhD, Peter G Vooijs MD, PhD

Summary

In this study cervical cancer mortality figures for the period 1936-1983 were evaluated. For the period 1950-1981 trends in age-specific rates were analysed by separating the variations attributable to age at death, period of birth and period of death.

Cervical cancer mortality decreased since 1960 and the decline was more rapid from about 1975 The organized screening, which started in 1976 could be responsible for the acceleration in the decline, but since the decline was already evident before screening commenced, other factors must play a role It seemed likely that a fall in incidence or an improvement of early diagnosis were responsible for the decline The cohort analysis showed an increased risk for younger age groups but since the observations were derived from one five-year age group no firm conclusions about future trends can be made yet.

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## Introduction

Reduction of the number of deaths due to cervical cancer is one of the main goals of cervical cancer screening programmes. Lack of randomized trials prevents a conclusive evaluation of the effect of screening and since cervical screening is widely accepted as a useful practice such a trial will never be performed.

In several countries cervical cancer mortality declined some years after the start of the screening programmes (1-8). The role of cervical screening in this decline is debated by some people, because cervical mortality already started to decline prior to the start of the screening programmes and furthermore was also observed in countries where cervical screening was not common (9)

In The Netherlands population screening started in 1976, relatively late in comparison with other countries. For this reason trends in cervical cancer mortality rates cannot be the consequence of the cervical screening programmes. In this study mortality figures for the period 1936-1983 are evaluated against the background of a possible "natural" trend in cervical cancer mortality.

## Populations and Methods

Data on the number of deaths due to cervical cancer as well as population data were derived from the Central Bureau of Statistics (10). This institution compiles the causes of death according to ICD-agreements. The data used in this study are based on death certifi-

cates which state cervical cancer as primary cause of death. Age-specific mortality figures were available for the calendar period 1936-1983.

Mortality rates were estimated with age-specific mid-year population numbers (age 25 and over). Comparisons were based on age-adjusted mortality rates and on mortality ratios. Tests of homogeneity were performed and 95% confidence limits were calculated (11). Graphs were smoothed by means of spline functions (12). For the calendar period 1950-1981 we were able to perform a cohort analysis. The log-linear model as described by Barrett was used to separate the variations attributable to age at death, period of birth and period of death (13). Each age-specific death rate was regarded as the product of three numbers - an age value, a period of birth value, and a period of death value. Each cohort was characterised by its central year of birth. Since knowledge of any two of age at death, period of birth, and period of death neccessarily implies knowledge of the third, these three factors are not statistically independent and some assumptions have to be made. We assumed that the period of death factor for 1977-1981 was zero and the factors for the period of birth 1881-1885 and 1886-1891 were zero. The model permits only conclusions about changes in trends not about linear trends. Cohort values relating to the earliest and latest years of birth were based on fewer age-specific death rates than the central cohorts. Thus in Figure 5 cohort values shown as points on the extreme left and right were derived from one five-year age group, those adjacent from two, and so on. This means

that the extreme points are statistically less reliable than the central ones. The extreme right ones were based on recent death rates in young women and may give an important clue for the future trend.

## Results

Crude mortality rates are summarized in Table 1. The crude rate is lower in the decade after world war II and in the past 15 years.

Table 1:
Cervical cancer mortality rates subdivided for 10 calendar periods and in absolute numbers per year (mean of the 10 years period)

| Calendar period | Mortality per 100.000 woman-years | Mean number of deaths per year |
|---|---|---|
| 1936-1939 * | 12.3 | 292 |
| 1940 1944 | 10.6 | 267 |
| 1945-1949 | 9.9 | 266 |
| 1950 1954 | 13.2 | 332 |
| 1955-1959 | 12.4 | 388 |
| 1960-1964 | 12.4 | 413 |
| 1965-1969 | 11.7 | 415 |
| 1970-1974 | 8.9 | 341 |
| 1975-1979 | 9.0 | 375 |
| 1980-1984 | 7.0 | 315 |

* calendar period of 4 years only

Crude rates are difficult to interpret since changes in age distribution can be responsible for trends. Mortality rates for 5-year age groups are displayed in frequency blocks in Figure 1. Mortality below 35 is low during the entire period.

In all the other age groups a dip at the end of world war II and immediately afterwards is visible and rates are declining since 1960. The decline is most evident in the age groups 35 through 54 years.

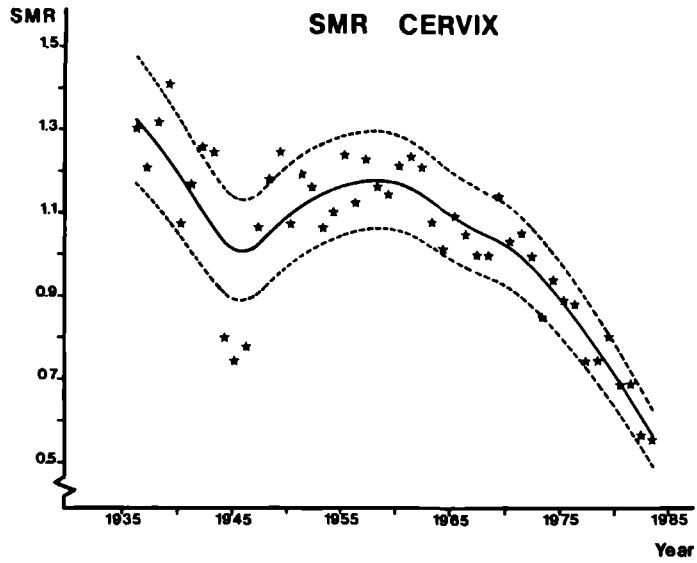


*Figure 1:* Cervical cancer mortality per 100.000 women years in The Netherlands 1936-1983 according to age group and calendar period.

To adjust for age, indirectly age-standardized mortality ratios (SMR's) were calculated for the period 1936-1983. The mortality rates of the Dutch sum population 1936-1983 were used as a standard. To check if a trend in mortality rates was similar in all ages, tests of homogeneity were done in each 5-year age group. In some years this test shows significant results, but one should not pay too much attention to this finding as the significant result was always the consequence of a deviant mortality rate in one age group. Mortality rates

are based on small numbers of cervical deaths in each age group. The calculated SMR's plus the corresponding 95% confidence limits are graphed in Figure 2. After this procedure the dip during world war II and the steep decline since 1960 are even more evident.

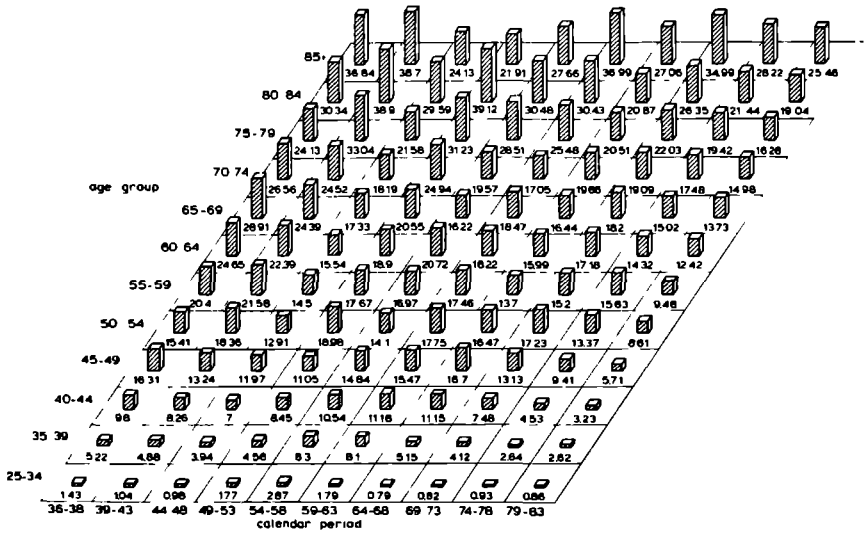


*Figure 2:* Standardized mortality ratios and 95% confidence intervals for cervical cancer in The Netherlands 1936-1983.

In Figure 3 age-specific mortality figures according to period of birth are graphed. Mortality is decreasing in the older birth cohorts. The birth cohorts from 1911 and 1916 show higher age-specific mortality rates than the cohorts born before. The cohorts of 1926 and 1931 show a strong decline in age-specific mortality.

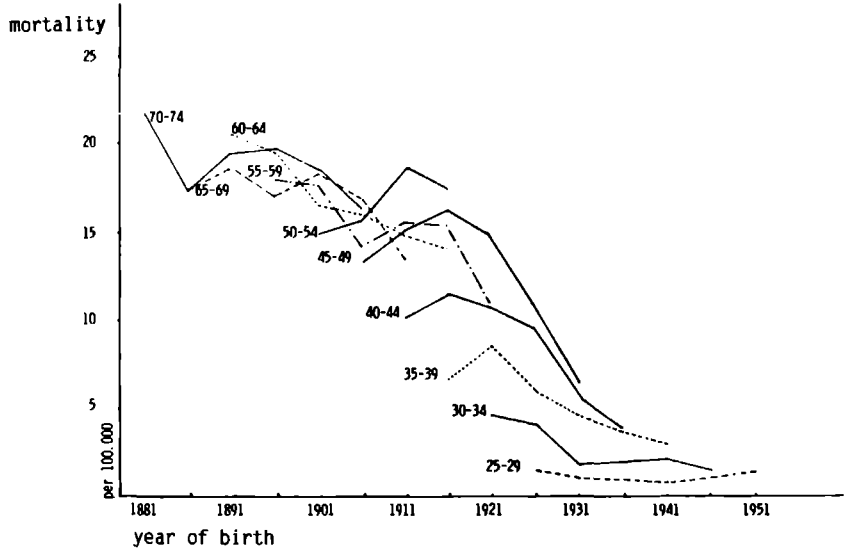


*Figure 3:* Age specific mortality rates according to year of birth. Mortality during 1950-1981.

In Figure 4 and 5 the age, time and cohort-factors are graphed. In Figure 4 the age value is plotted against age at death. Mortality increases with increasing age. In Figure 5 cohort values are plotted against central year of birth. If the cohort values are interpreted in terms of birth there was an increase until the 1926 cohort. After this there was a decrease till the 1941 cohort. The cohort value of the youngest cohort increases but this value is based on only one five-year age group. There is a gradual decline in the period of death values.

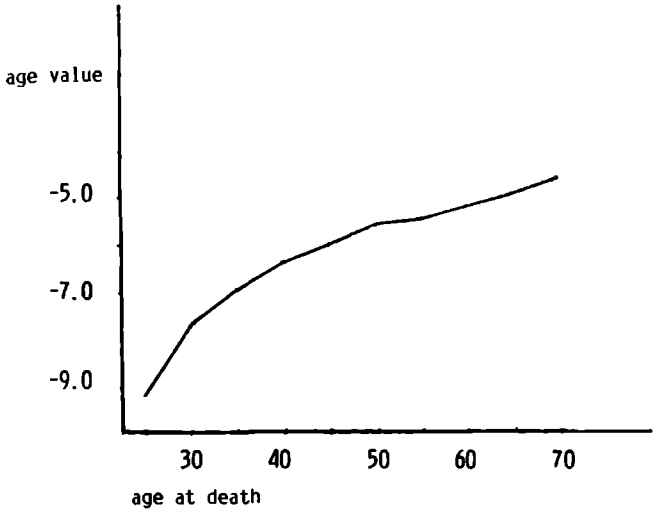


*Figure 4:* Age values. Mortality during 1950-1981.


*Figure 5:* Cohort and period of death values. Mortality during 1950-1981.

Discussion

Organized screening on a large scale started in The Netherlands in 1976 Before that year there was one pilot study in the city of Utrecht and adjacent communities (14) Before 1970 cervical screening was rare and a smear was made only for medical reasons The effect of screening on mortality rates can be expected from about 10 years after the introduction of screening Possibly the substantial acceleration in the mortality decline at the beginning of the 1980 s could be due to the early detection programmes, but it is not possible that the mortality decline since the early 1960's is the result of organized screening Therefore other factors must play a role in the decline Such factors may be related to either registration errors, a fall in the incidence of cervical cancer, improved therapy or a combination of these

Percy et al compared the hospital diagnosis with the diagnoses given in the death certificates (15) As far as cervical cancer is concerned, 80 percent of these cancers were correctly reported on the death certificates as cervical cancers, whereas 10 percent was reported as cancer of the corpus Even when the accuracy of death certificates in The Netherlands would be less, it is not likely that it became even worse in recent years The dip at the end and immediately after world war II is most probably due to registration failures

Prior to 1970 about 50% of all deaths due to cervical cancer were reported on the death certificates as cancer of the uterus which was not further specified, but after 1970 registration improved (10) When

correcting for this relatively large number of not further specified cancers of the uterus the decline in mortality rates after 1960 would even be more steep than is shown in Figure 2.

If the fall in mortality should reflect a fall in incidence, what factors could have produced it? In studies about the etiology of cervical cancer the most significant risk factors are early sexual intercourse and promiscuity (16-20). There is no evidence that in the last decade women have begun to delay first intercourse or have become less promiscuous. The hypothesis that cervical cancer is a venereal disease, is not yet supported by mortality trends in The Netherlands. In England Osmond concluded from the results of a cohort study that the women born after 1945 were at higher risk for cervical cancer (21). In the cohort analysis of Dutch mortality data for cervical cancer an increased risk for younger age groups was found.
However one has to keep in mind that mortality rates for the women born after 1945 are only available till they have a maximum age of 40 years. Therefore firm conclusions about a significant change in mortality rates in women born after world war II are not yet possible. Contrary to what has been reported for the United Kingdom, no significant increase in morbidity from cervical cancer in women below 35 years of age has become evident in The Netherlands (22).
A possible explanation for the fall in incidence is improved genital hygiene, which might reduce the risk of an etiologic infective agent being transmitted.

Apart from a decrease in incidence, the fall in mortality rates could be due to more effective treatment. A slight improvement in therapy has been documented but this change is still too small to account for the rather dramatic decline in cervical mortality (23).

Probably the diagnosis of invasive cancer in a less advanced stage could also be of influence. Since there is no national cancer registry in The Netherlands, data about the incidence and the distribution of the different clinical stages of invasive cervical cancer are not available to support this view.

The rising hysterectomy rate could also be an important cause for the decline in cervical cancer mortality, but Lyon and Miller showed that the increase in hysterectomy rates in the United States and Canada was not sufficient to explain the decreases in mortality rates which have occurred during the same period in cancers of the cervix (24-26). In The Netherlands the increase in the number of hysterectomies started in the seventies. Bosman et al showed that over the years 1975-1978 only 6% of the decrease of mortality due to cervical cancer can be attributed to the increased frequency of the hysterectomy rate (27). It is likely that, if the number of hysterectomies continues to rise at the present state, the impact on the decline in cervical mortality rates will become more important.

Analysis of Dutch cervical mortality rates showed a decline in the number of deaths due to cervical cancers. Neither cytological screening nor an increased rate of hysterectomies nor improved therapy can

be considered responsible for this decline; a fall in incidence because of better genital hygiene or an improvement of early diagnosis seems the most reasonable explanation. Till now no data are available to sort out which one of these explanations is responsible for the ongoing decline in cervical cancer mortality.

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*CHAPTER 2*

# *CERVICAL CANCER SURVIVAL IN NIJMEGEN REGION, THE NETHERLANDS, 1970-1985**

Yolanda van der Graaf MD, Petronella GM Peer MSc, Gerhard A Zielhuis MSc, PhD, Peter G Vooijs MD, PhD

Summary

For 359 women, diagnosed between 1970 and 1985 with invasive cervical cancer, survival rates were computed The 5-year survival rate for the entire group was 67% Survival was better in the period 1976-1980 Extension of the tumor and age at diagnosis were important prognostic factors. The effects of clinical stage, age at diagnosis and year of diagnosis were studied simultaneously with the proportional hazards model. The hazard rate increased with increasing age and increasing clinical stage Only in case of IIB tumors year of diagnosis had effect on survival For the other clinical stages there was no significant effect on survival of year of diagnosis.

## Introduction

Cervical mortality rates are declining in several Western countries (1) In The Netherlands cervical cancer mortality decreased since

**Submitted*

1962 Since cervical cancer screening programmes in The Netherlands did not start before 1976, cervical screening cannot be an explanation for this decline

A fall in incidence of cervical cancer or a shift towards diagnosis of invasive cervical cancer in a less advanced stage seems the best explanation for this "natural" decline However improvements of therapy with a better patient survival could also be at least for some part responsible for the decrease in mortality from cervical cancer. Ketting computed survival rates for all patients with invasive cancer of the uterine cervix treated in a large municipal hospital for the calendar period 1950-1979 (2) He reported an improvement in therapeutic results in patients with stage I, II and III of cervical cancer. He proposed the change in the treatment scheme in the period 1961-1969 as an explanation for the decrease in mortality. In this study we evaluated the survival of cervical cancer patients in Nijmegen region in the calendar period 1970-1985 in order to investigate improvement in therapeutic results in the last 15 years.

## Patients and Methods

Population screening for cervical cancer started in 1976 in three pilot regions in The Netherlands In these regions a quarter of the Dutch population is living All women aged 35 through 54 were invited every three years for a cervical smear. Apart from the screening programme an increasing number of smears is made by general practition-

ers and gynecologists. In the region of Nijmegen (about 750.000 inhabitants) data on the incidence of invasive cervical cancer were available from the local cancer registry which has been kept since 1970 (3). From the files of all pathology laboratories in the region all women were registered with a histological diagnosis of microinvasive or invasive cancer of the uterine cervix. If a histological diagnosis was made in a pathology laboratory outside the region this diagnosis will not become available for registration but such cases were exceptions.

Items registered were age at diagnosis, date of diagnosis and clinical stage of the cervical cancer. Classification of the extension of the tumor is done according to the FIGO classification (4).

All diagnoses of cervical cytological smears made in the screening programme as well as by general practitioners and gynecologists were added to the registry of histological diagnoses.

All patients known with cervical cancer were followed for vital status with the help of the registrar's offices and the Central Bureau of Statistics. For a few cases this information was obtained directly from gynecologists and general practitioners. Since at the time the study was terminated several patients were alive and other patients were lost to follow up, survival curves were computed according to the technique of Kaplan-Meier (5). Death from other causes is considered censoring. The standard errors of the estimated survival rates were computed according to the Greenwood formula (6). To test the equality of survival curves for different groups, the Mantel log-rank test was used (7).

In order to asses the effect of clinical stage of disease, age at diagnosis and year at diagnosis simultaneously we used the proportional hazards model according to Cox (8).

## Results

During the study period 378 women were diagnosed with invasive cervical cancer. Of 10 women no follow up data could be traced and of 9 women clinical stage of the tumor remained unknown. These women were left out of the analysis. In Table 2 clinical stage distribution according to age and point of time at diagnosis for the remaining 359 women is summarized.

Table 2:
Clinical stage distribution according to age and calendar period

| | Clinical stage | | | | | | |
|---|---|---|---|---|---|---|---|
| Age | IA N | IB N | IIA N | IIB N | III N | IV N | Total |
| < 54 | 71(35%) | 54(26%) | 18(9%) | 31(15%) | 23(11%) | 8(4%) | 205 |
| ≥ 55 | 13(8%) | 28(18%) | 12(8%) | 51(33%) | 42(27%) | 8(5%) | 154 |
| Calendar period | | | | | | | |
| 1970-1975 | 27(19%) | 35(24%) | 13(9%) | 41(28%) | 23(16%) | 6(4%) | 145 |
| 1976-1980 | 38(28%) | 25(18%) | 14(10%) | 28(20%) | 27(20%) | 5(4%) | 137 |
| 1981-1985 | 19(25%) | 22(29%) | 3(4%) | 13(17%) | 15(19%) | 5(6%) | 77 |

The Kaplan-Meier survival curve for the total group of women is displayed in Figure 6. Five-year survival was calculated at 67.4% (standard error 2.6%). This plot illustrates that 5-year survival is a good

parameter for survival since only a few women die from cervical cancer after the fifth year.

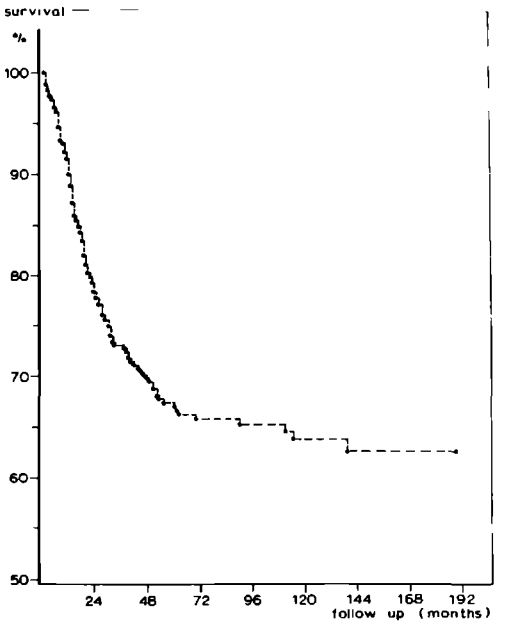


*Figure 6:* Survival curve of women with cervical cancer. Region of Nijmegen, The Netherlands, 1970-1985.

Table 3 shows the effect of extension of the tumor, age and calendar period on 5-year survival.

Table 3:
Survival rates according to clinical stage, age group and calendar period

| | | | | | | |
|---|---|---|---|---|---|---|
| | Clinical stage (FIGO) | | | | | |
| 5-year survival | IA | IB | IIA | IIB | III | IV |
| | 97% | 77% | 83% | 55% | 36% | 11% |
| | Age group | | | | | |
| 5-year survival | <35 | 35-54 | | 55-70 | | >70 |
| | 91% | 72% | | 60% | | 34% |
| | Calendar period | | | | | |
| 5-year survival | 1970-1975 | | 1976-1980 | | 1981-1985 | |
| | 62% | | 72% | | 67% | |

In general women with less advanced stages have a better survival Exceptions are women with cervical cancers in clinical stage IIA. These women had a better survival then women with clinical stage IB tumors, although not significant (Mantel log-rank test p=0.52). All other pairwise comparisons yielded significant results with the log-rank test. Survival curves for each stage are plotted in Figure 7.

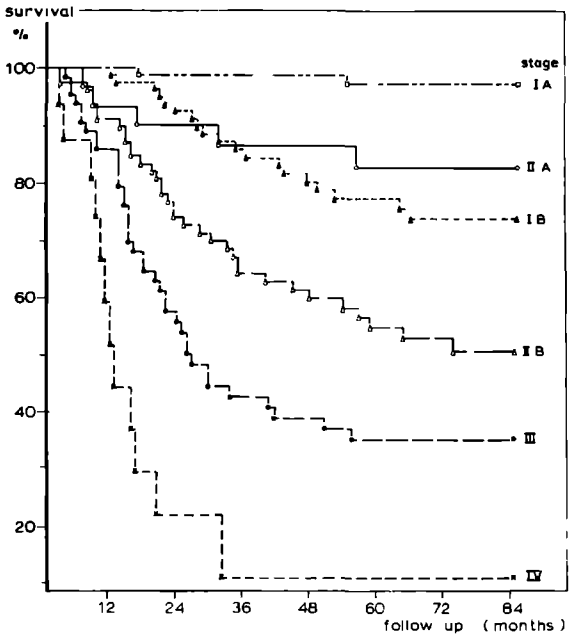


*Figure 7:* Survival curves of women with cervical cancer according to clinical stage Region of Nijmegen, The Netherlands, 1970-1985

Survival rates differed also between age groups as is shown in Table 3. Survival was better in younger women. Although survival rates

differed significantly between the three calendar periods, they do not show a trend. To study the effect of clinical stage, age at diagnosis and year of diagnosis simultaneously, these three factors were incorporated into the proportional hazards model according to Cox. This multivariate regression model takes into account the correlation between the three factors.

Because it was unlikely that for the same tumor stage, improvement of therapy differed for different ages and that the effect of age on survival was different for the various clinical stages, we did not take into account interaction of age with year of diagnosis and tumor stage. It could be, however, that only for some clinical stages therapy improved in the course of time For that reason, age at diagnosis, clinical stage, year at diagnosis and the interactions of clinical stage and year of diagnosis were entered in the model Only in clinical stage IIB the effect of year of diagnosis was significant and so in the final model age at diagnosis, clinical stage and the effect of year at diagnosis in clinical stage IIB were entered (Table 4)

Table 4
Regression coefficients for clinical stage, age at diagnosis and the effect of year of diagnosis in stage IIB in Cox's proportional hazards model

| Variables | | Regression coefficients | Standard error | Quotient | P-value one-sided |
|---|---|---|---|---|---|
| Age at diagnosis reference age 50 | | 0.018 | 0 0078 | 2 34 | 0.0097 |
| Year of diagnosis in stage IIB reference 1975 | | -0.10 | 0 0467 | 2 20 | 0 0137 |
| Clinical stage reference IB | IA | -2.30 | 0 7421 | 3 10 | 0.0009 |
| | IIA | -0 33 | 0 4635 | 0 70 | 0 2408 |
| | IIB | 0 65 | 0 2820 | 2 32 | 0 0102 |
| | III | 1 26 | 0 2762 | 4 59 | 0 0000 |
| | IV | 2.20 | 0 3716 | 5 92 | 0.0000 |

Increasing age and increasing clinical stage gave a significant higher mortality. For stage IB and IIA, however, there was no significant difference in survival. For women with a stage IIB tumor survival improved in the course of years. Comparison of the different survival curves predicted from the model with the Kaplan-Meier survival estimates revealed a good fit.

## Discussion

The overall 5-year survival rate calculated in this study population is comparable with survival rates reported by others (2 9 10). The "extension" (clinical stage) of the tumor seems the best predictor of survival.

Less advanced clinical stages with better survival were more frequently diagnosed in young women. Only part of these better survival rates in the youngest age groups can be explained by this phenomenon since after correcting for clinical stage the effect of age remained. Only for women with a stage IIB tumor survival improved significantly during the last 15 years. Survival rates for these women became in the 1980's as high as for women with IB and IIA tumors, while in the period before 1980 5-year survival was calculated at 46%. This gain in life expectancy must be the result of improvement in radiotherapeutic treatment since all women with a stage IIB tumor were treated with radiation therapy with curative intent. This finding is comparable with the results described by Ketting (2). In that

study 5-year survival was 40% for stage IIB patients in the period 1961-1969 and 70% in the period 1970-1974 and comparable with the 5-year survival rate in stage IIA patients. The 5-year survival rate for cases with a IB tumor was in our study somewhat lower than reported by Ketting (2). In his study the 5-year survival for these cases was 84% in the period 1970-1974. Possibly this difference can be explained by the fact that the study populations were not comparable. Our study was population-based and the women were treated in the regional hospitals and in one university hospital, while in the study of Ketting all women were treated in a center.

The population screening led to a decrease of the incidence of invasive cervical cancer. In the period prior to the population screening programme (1970-1976) the yearly incidence of invasive cervical cancer was 18.6 per 100.000 in women aged 35 through 54 years. During the first screening period the incidence was 21.5 per 100.000 women, in the second screening period 9.0 per 100.000 women and in the third screening period 3.3 per 100.000 women. The incidence of invasive cancer among women older than 54 years, who were not included in the cervical cancer screening programme, showed a decline 6 years after the start of the programme. This can be explained by the increasing percentage of women in this age group who in previous years, were eligible for the cervical cancer screening programme and hence received treatment when a preinvasive lesion was discovered.

In the course of 15 years a shift to more favourable clinical stages became evident. This shift to less advanced stages of cervical cancer at diagnosis and the improvement of therapy for women with a stage IIB tumor are responsible for a better overall survival. For the other clinical stages survival did not improve significantly during the last 15 years.

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*CHAPTER 3*

# *POPULATION SCREENING FOR CERVICAL CANCER IN THE REGION OF NIJMEGEN, THE NETHERLANDS 1976-1985**

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Summary

In this study the results of 9-year cervical screening in the region of Nijmegen, The Netherlands are presented.

All women aged 35 through 54, were invited every three years for a cervical smear. Overall attendance rates were 74%, 67% and 63% at first, second and third screening respectively. The number of histologically confirmed severe epithelial abnormalities discovered in women who were screened for the first time was 3.8 per thousand smears, 1.0 per thousand in women who were screened twice and 0.7 per thousand in women who were screened three times in the programme.

Three years after the start of the screening programme the incidence of invasive squamous cell cancer started to decline in the women aged 35 through 54 years. On the basis of the results of this study we may conclude a screening policy with an interval of three years to be a safe procedure. Whether this interval is the most efficient cannot be

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concluded. We have the impression that an interval of four to six years may lead to comparable results.

## Introduction

In The Netherlands 300 deaths per year are due to cervical cancer and about 1200 new cases of invasive cervical cancer are diagnosed every year. The incidence of cervical cancer in The Netherlands is comparable with the incidence in other Western countries and relatively low compared to other cancer types. After promising results of cervical screening in other countries (1-4) cervical screening was initiated in The Netherlands in 1976.

Screening was initiated by the government as pilot projects in different regions to evaluate the effectiveness of screening for cervical cancer and to assess the best organisation scheme for a nationwide screening programme. When screening should prove to be effective it should be implemented in general practice.

Since politically it proved to be unacceptable to offer this screening facility to a part of the population only, few years after the start of the screening programme in the pilot regions, screening was introduced in the entire country.

Effectiveness should be assessed by comparing morbidity and mortality figures in the three pilot regions with the other regions in The Netherlands.

In this study we present the results of 9-year cervical screening in one of the pilot regions, the city of Nijmegen and its environments.

Populations and methods

The entire screening programme comprised nine years subdivided in three periods of three years each Every three years all women aged 35 through 54 were invited for a cervical smear. The invitations were sent by the registrar's offices of the 62 municipalities which participated in the screening programme The programme got quite some publicity and in the local papers women were urged to attend the screening.

The smears were made by experienced smear-takers in a mobile van which was driven to the municipalities where the women were living. Before the smear was made several questions were asked about the number of pregnancies, menstrual history and the method of contraception.

All smears were processed at the Cytopathology Laboratory of the Department of Pathology, University of Nijmegen and screened by experienced cytotechnologists. Cytological findings were recorded in terms of the Papanicolaou classification, to which a description of cytological findings in the smear was added. Each descriptive diagnosis comprised 4 terms indicating· 1. the cellular composition of the smear 2. the presence or character of inflammatory changes 3. the expected histopathologic change in the squamous or squamous meta-

plastic cervical mucosa 4. changes in columnar cells from the endocervical mucosa or an abnormality related to the endometrium. In case of an abnormal cervical cytological finding the general practitioner was contacted who was responsible for the recommended follow up.

When the cytological diagnosis was consistent with a severe dysplasia, a carcinoma in situ or an invasive cancer, the general practitioner was asked to refer the woman to a gynecologist. In case of a cytological diagnosis consistent with a slight or a moderate dysplasia, the general practitioner was requested to make a repeat smear after six or three months respectively. The laboratory checked whether the advice was followed and if not, the general practitioner was contacted and reminded of the recommended follow up. All cytological and histological diagnoses from women participating in the screening programme were collected from pathology laboratories serving the area and linked with the cytological diagnosis of the population screening smear.

Diagnosis and treatment of cervical abnormalities is not yet uniform in The Netherlands. For confirmation of cytological diagnoses, random biopsies, biopsies directed by colposcopy, curettings, cone biopsies and sometimes hysterectomies are performed. Recently random biopsies are increasingly replaced by biopsies directed by colposcopy.

## Results

*Attendance rate*

Overall attendance rates were 74%, 67% and 63% at first, second and third screening respectively.

In the course of the nine year screening programme attendance rates declined in all age groups but the youngest (35 through 37 years). These women were invited in second and third screening period for the first time.

Attendances rates were lower with increasing age and differed substantially in the 62 communities In urban communities attendance rates were considerably lower compared to rural areas Unmarried, divorced, as well as widowed women were less likely to participate.

*Cytological results*

In Table 5 the cytological results of first, second and third screening are summarized As expected the number of severe epithelial abnormalities was highest at first screening. At first screening quite a number of women had a cytological smear taken for the first time in their life (57%). The percentage of severe epithelial abnormalities at second and third screening was almost the same Compared to the first screening period the number of cervical smears suspicious of (micro)invasive squamous cell cancer declined considerable at successive screenings. At first screening the number of severe epithelial abnormalities was highest in women aged 53 through 55 years. At second and third screening the number of severe epithelial abnormalities was equally distributed over the different 3-year age groups. However this reduction in the number of severe epithelial abnormalities

was not seen in the age group of women 35 through 37 years who in each three year screening period were invited for the first time

The number of smears with a cytological diagnosis consistent with moderate dysplasia was increased after the first screening period. However this is partly due to changes in diagnostic procedures in the laboratory

Table 5
Distribution of epithelial abnormalities in cervical smears from women participating in the screening programme

| Cytological diagnosis consistent with | Screening period: First N % | Second N % | Third N % | Rank of smear (3-year interval): 1 N % | 2 N % | 3 N % |
|---|---|---|---|---|---|---|
| No abnormalities Slight atypia Slight dyslasia | 62 244 99 5% | 57 360 99 5% | 54 360 99 5% | 44 384 99 0% | 51 669 99 6% | 22 067 99 7% |
| Moderate Dysplasia | 118 0 19% | 181 0 32% | 150 0 27% | 98 0 22% | 144 0 28% | 38 0 17% |
| Severe dysplasia and Carcinoma in situ | 164 0 26% | 126 0 22% | 125 0 23% | 153 0 34% | 84 0 16% | 31 0 14% |
| (Micro)invasive cancer | 25 0 04% | 5 0 009% | 2 0 004% | 22 0 05% | 2 0 004% | - |
| Total | 62 551 100% | 57 672 100% | 54 637 100% | 44 657 100% | 51 899 100% | 22 136 100% |

In the same table the cytological results of first, second and third smears are compared The figures illustrate clearly the effect of previous screenings In first cervical smears severe epithelial abnormalities were discovered in 3 9 per thousand smears, in second smears in

1.7 per thousand smears and in third smears in 1.4 per thousand smears. This means a reduction in the number of severe epithelial abnormalities by more than 100% diagnosed in second and third smears compared to the number found in first smears.

In 51.899 women who were screened twice in only two women the second smear was suspicious for (micro)invasive cancer In women who were screened three times not one smear was found to be suspicious for (micro)invasive cancer at third screening.

Changes in the number of smears consistent with moderate dysplasia are difficult to interpret since the diagnostic laboratory procedure was changed during the years of the screening programme towards a higher sensitivity for slight to moderate epithelial changes However in women who were screened three times a tendency to a lower incidence of moderate dysplasia was seen in comparison to those women who were screened twice.

*Tissue diagnosis and predictive value.*

During the screening programme 447 women were referred to a gynecologist because of a cytological diagnosis consistent with a severe epithelial abnormality.

Follow up diagnoses in these women are summarized in Table 6.

Table 6
Follow up diagnosis after cytological diagnosis consistent with severe dysplasia, carcinoma in situ and (micro)invasive cancer

| Follow up diagnosis | Screening period First 1-8-1976/ 31-7-1979 | Second 1-8-1979/ 31-7-1982 | Third 1-8-1982/ 31-7-1985 | Total |
|---|---|---|---|---|
| No abnormalities<br>Slight atypia or<br>Slight to moderate dysplasia | 17 | 27 | 29 | 73<br>16% |
| Severe dysplasia<br>Carcinoma in situ | 118 | 85 | 63 | 266<br>60% |
| (Micro)invasive cancer | 34 | 4 | 3 | 41<br>9% |
| Repeat smear only | 17 | 15 | 26 | 58<br>13% |
| No follow up available | 3 | - | 6 | 9<br>2% |
| Total | 189 | 131 | 127 | 447 |
| Predictive value<br>Cytological diagnosis ≥ severe dysplasia | 82% | 68% | 55% | 70% |

Of 9 (2%) women follow up diagnosis was not yet available at the conclusion of this study.

In 58 (13%) women follow up was limited to a repeat smear. In these smears no abnormalities were found and tissue diagnosis was not considered necessary These women were further followed by repeat cytological smears In 73 (16%) women the tissue diagnosis showed none or only slight epithelial abnormalities. In 307 (69%) women the severe abnormality was confirmed at histological diagnosis. The predictive values for the different screening periods for severe epitheli-

al abnormalities, severe dysplasia, carcinoma in situ and (micro)invasive cancer were 82% at first screening, 68% at second screening and 54% at third screening This decline in predictive value is a consequence of the decreasing number of severe epithelial abnormalities in a screened population (5).

When a cytological diagnosis of a smear was consistent with moderate dysplasia, a repeat smear after three months was advised When the cytological diagnosis of such a repeat smear was comparable with the first diagnosis or suggested a more severe lesion the women were referred to a gynecologist. In Table 7 'final' diagnoses of women with smears consistent with moderate dysplasia are summarized.

Table 7
"Final" diagnosis after cytological diagnosis consistent with moderate dysplasia

| Follow up diagnosis | Screening period First 1-8-1976/ 31-7-1979 | Second 1-8-1979/ 31-7-1982 | Third 1-8-1982/ 31-7-1985 | Total |
|---|---|---|---|---|
| No abnormalities Slight atypia or Slight to moderate dysplasia | 28 | 20 | 29 | 77 17% |
| Severe dysplasia Carcinoma in situ | 30 | 40 | 14 | 84 19% |
| (Micro)invasive cancer | 2 | 3 | - | 5 1% |
| Adenocarcinoma | | | 1 | 1 0.2% |
| Repeat smear only | 56 | 110 | 90 | 256 57% |
| No follow up available | 2 | 8 | 16 | 26 6% |
| Total | 118 | 181 | 150 | 449 |
| % of women with severe abnormality at histological diagnosis | 28% | 25% | 10% | 22% |

During the screening programme in 449 women a cytological diagnosis consistent with moderate dysplasia was made.

Of 26 cases (6%) follow up is not (yet) available. In 167 women (37%) repeat cytological diagnosis was followed by histological examination of the cervix In 90 women (21%) of the total group a severe epithelial abnormality was diagnosed

If we calculate the percentage of severe abnormalities in the group women with a cytological diagnosis consistent with moderate dysplasia, the conclusion can be drawn that the percentage of severe epithelial abnormalities is reduced from 28% during the first screening to 25% during the second screening period and to 10% during the third screening period. Finally in 5 women after an initial cytological diagnosis "moderate dysplasia" at follow up invasive cancer was diagnosed The smears of these five women were reviewed, three smears were not correctly screened Review diagnosis was consistent with severe dysplasia (screening error). The review of the other smears did not alter the cytological diagnosis consistent with moderate dysplasia It can be concluded that the sample was inadequate (sample error).

Of 46 invasive cancers (41 after a cytological diagnosis consistent with severe dysplasia and 5 after a cytological diagnosis consistent with moderate dysplasia) 28 were found to be microinvasive (IA, with an invasion depth less than 5 mm), 7 cancers were found in clinical stage IB, 4 were found in stage IIA, 3 cancers were in stage IIB and 1 cancer was in stage III. In three women clinical stages were unknown

*Treatment*

For women who had a cytological diagnosis consistent with severe dysplasia, carcinoma in situ and (micro)invasive cancer (N = 353) during the first seven years of the population screening programme, we registered what final treatment was given. Six women were already known with cervical abnormalities before they participated in the population screening programme and of six women no follow up results could be traced. In Table 8 final treatment according to tissue diagnosis is given for the remaining 341 women

Table 8
Therapy according to previous histological diagnosis

| Histological diagnosis | Therapy | | | | | | |
|---|---|---|---|---|---|---|---|
| | None | Ablatio biopsies | Conisation | Hysterectomy | Radical hysterectomy | Radiotherapy | Total |
| No or only slight abnormalities | 19 | 4 | 7 | 10 | - | 1 | 41 |
| Moderate dysplasia | 7 | | 2 | 14 | | | 23 |
| Severe dysplasia Carcinoma in situ | 10 | 9 | 14 | 160 | 1 | 3 | 197 |
| (Micro)invasive cancer | - | - | 1 | 8 | 7 | 9 | 25 |
| No histological diagnosis | 37 | - | 3 | 15 | - | - | 55 |
| Total | 73<br>21% | 13<br>4% | 27<br>8% | 207<br>61% | 8<br>2% | 13<br>4% | 341<br>100% |

The therapy which was applied most frequently was simple hysterectomy (61%). In three women conisation was performed without previous histological diagnosis, because the conisation was performed for diagnostic reasons. The same explanations can be given for conisations after none or only slightly abnormalities of the cervix; the conisation was part of the diagnostic procedure.

In case of the 15 women, who received hysterectomy without previous histological diagnosis, it is likely that there was done histological examination of the cervix but the results could not be traced. Sometimes a serious discrepancy between cytological diagnosis and histological diagnosis was the reason for hysterectomy. Radiotherapy is the therapy of choice in case of invasive squamous cell cancer, clinical stage IIB, III or IV. In some other cases radiotherapy was chosen because the macroscopic view at laparotomy and the general state of health which was too bad to perform hysterectomy. Since it was not possible to evaluate other factors which could have influenced therapy choice, the interpretation of the figures is difficult. The ablatio is a therapy, which is yet only performed in one hospital in the region, but which is likely to become the treatment of choice in future for histologically confirmed severe dysplasia and carcinoma in situ. There is a growing awareness among gynecologists that conisations formerly considered to be the treatment of choice for severe epithelial abnormalities might be considered as overtreatment. A protocol for a more conservative surgical approach for these intraepithelial lesions is presently under consideration.

## Discussion

When analysing the number of severe epithelial abnormalities diagnosed in women who participated twice or three times in the screening programme, it becomes evident that screening with a 3-year interval is effective in reducing the prevalence of severe epithelial lesions.

In Table 9 the number of severe epithelial abnormalities, confirmed by histological diagnosis, per thousand cytologically screened women is summarized At first screening severe abnormalities were diagnosed in 3.0 per thousand. At second screening in 2.3 per thousand and at third screening only in 1 5 per thousand cytologically screened women.

Table 9
Histological diagnosis. Number of histological diagnoses with severe dysplasia, carcinoma in situ and (micro)invasive cancer per thousand cytologically screened women

| | Tissue diagnosis | Number of screened woman | Per thousand |
|---|---|---|---|
| Screening period | Severe dysplasia Carcinoma in situ (Micro)invasive cancer | | |
| First | 185 | 62.551 | 3.0 |
| Second | 133 | 57.672 | 2.3 |
| Third | 80 | 54 637 | 1.5 |
| Rank of smear (3-year interval) | | | |
| First | 169 | 44.657 | 3.8 |
| Second | 54 | 51 899 | 1.0 |
| Third | 15 | 22.136 | 0.7 |

When comparing the number of severe abnormalities found in women who were screened for the first time with the number found in women who were screened twice or three times with an interval of three years, the reduction was even greater; 3.8 per thousand in first smears, 1.0 per thousand in second smears and only 0.7 per thousand in third smears. On the basis of these findings we may conclude a screening policy with an interval of three years to be a safe procedure. Whether this interval is the most efficient cannot be concluded. We have the impression that an interval of four to six years may lead to comparable results.

A small number of women (N = 4435) was screened twice with an interval of six years (participation in first and third screening round). The number of severe epithelial abnormalities in second smears in these women was equal to that in women who were screened twice with an interval of three years. However the number of women screened with an interval of 6 years is still too small for definite conclusions.

To assess the effectiveness of a cervical screening programme, it is not sufficient to register disease processes in the population who joined the programme The number of women with a previous negative smear and an abnormality diagnosed some time later outside the programme should be known as well. Furthermore it should be checked whether the right population was screened. To address the first problem we checked for all women registered in our cancer registry if

they participated in the population programme and if so we linked the cytological result with the information registered in the cancer registry. In two successive screening periods of three years each 120.223 smears were made. Within 48 months after a negative cytological smear 45 women were entered in the cancer registry with a histological diagnosis of a severe epithelial abnormality of the uterine cervix. The number of true positives in that same period was 235 thus the sensitivity could be assessed at 84%. Of course this is an estimate which bears some inaccuracies but it is a good indicator of the quality of the test (6). In order to verify whether we screened the right population we monitored the incidence of invasive cervical cancer in the entire population

In the period prior to the population screening programme (1970-1976) the yearly incidence of invasive cervical cancer was 18.6 per 100.000 in women aged 35 through 54 years. During the first screening period 21.5 per 100.000 women, in the second screening period 9.0 per 100 000 women and 3 3 per 100.000 women during the third screening period (7). Thus some years after the introduction of population screening the incidence of invasive cervical cancer dropped considerably This decline is not only a consequence of the screening programme since also outside the screening programme a considerable number of smears was made for preventive reasons by general practitioners and it is impossible to separate the effect of the regular screening programme and the latter activity of general practitioners. During the first screening period (1976-1979) 86% of women aged 35

through 54 years had at least one smear made by a general practitioner or gynecologist or within the screening programme.

During the second screening period (1979-1982) 80% of the female population had at least one smear made in or outside the organized programme (7). Summarizing, the conclusion is justified that the Dutch screening programme proved to be effective in reducing morbidity due to cervical cancer and could be compared with the succesful programmes which were carried out in the Scandinavian countries (8-11). On the basis of the preliminary results of the three pilot screening projets the Dutch government decided that cytological screening for cervical cancer should be implemented in the general practice. An accurate registration system, proper follow up of abnormal smears and a good quality control of cytological smears and laboratory procedures are conditions for an effective screening programme. The failure of the cervical cancer screening programme in the United Kingdom was attributed to several of the above mentioned factors (12-14). Several questions remain unanswered, such as the optimal screening interval and should women below 35 years of age be screened periodically. A large study coordinated by the International Agency for Research on Cancer, and based on ten screening programmes in different parts of the developed world revealed that the risk of invasive cancer during the first 2 years after a negative smear was low compared to the risk prior to screening. The protection decreased gradually but some protection was seen up to ten years after the cytological smear (15). Invasive cancer below the age

of 35 is rare and mortality from cervical cancer below the age of 35 year is extremely low. Since the objective of screening for cervical cancer is to prevent invasive disease, extending the programme to younger ages does not seem necessary at this moment. The number of invasive cancers below the age of 35 years should be monitored and the screening policy should be reviewed regularly for its validity.

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*CHAPTER 4A*

# *THE EFFECTIVENESS OF CERVICAL SCREENING. A POPULATION-BASED CASE-CONTROL STUDY**

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Summary

The cervical smear history of 36 women with invasive cervical cancer was compared to that of 120 age-matched controls, drawn from local registrar s offices

Of the cases 47% were screened at least once, while of the controls this figure was 68%. The relative risk of getting invasive cervical cancer for women ever screened compared to women who were never screened was 0 32 The most important confounder was age at first intercourse Contrary to other studies however, we noticed that women who were younger when having first intercourse were screened more often. After correcting the relative risk screened versus unscreened for age at first intercourse the relative risk became 0 22. When the length of the interval since the last smear was considered, the relative risk was 0 18 when the smear was made between 2 and 5 years ago and 0.30 when this smear was made more than 5 years ago.

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This study supports the assumption that screening is effective in the prevention of invasive cancer of the uterine cervix. Even a screening interval of more then 5 years gives a considerable protection.

## Introduction

The evidence suggesting the effectiveness of cervical screening in reducing the occurence of cervical cancer is impressive (1-7). Most studies however are based on comparisons of incidence and mortality rates between populations with different screening intensity. Comparisons were made either between countries or regions for a given time period, or were done within a particular population group in different time periods. Since in these studies serious bias may have occurred, a causal relationship between cervical screening and a reduced risk for invasive cervical cancer has been questioned for a long time. Basically the problem can be defined as the lack of a properly designed randomized controlled trial. Such a trial has never been performed and never will be, because cervical screening has already been widely accepted by the public and by the health authorities as a useful practice. Once a form of screening has become wide spread, the case-control study can be used to monitor the effectiveness of the screening programme (8). Clarke and Anderson (9) and later La Vecchia et al (10) and Aristizabal et al (11) performed case-control studies in which women with invasive cervical cancer were compared to healthy controls in respect to their screening history. These stud-

ies were critisized on methodological grounds (12-14) In two of the above mentioned studies, women with microinvasive cancer were included in the case-group (9 11). In one study women with carcinoma in situ and microinvasive cancer were included in the case-group (10) Carcinoma in situ and microinvasive cancer are symptomless and thefefore only detectable by active, early recognition procedures such as screening

Consequently, a screened population will have a higher rate of any disease manifestation discovered during the lead-time interval, the period between the time that the disease is detected by screening and the time that diagnosis would have occured in the absence of screening Thus, if a person is considered to be a case on the basis of a characteristic of disease that comes to attention during the lead-time interval, there will be an excess of screen-detected cases, and a beneficial effect of screening could be obscured (12) We performed a case-control study which largely overcomes this deficiencies by excluding the preclinical cervical cancers. Only the more advanced stages of cervical cancer were included. In this study too, the objective was to analyse failure to participate in a screening programme as a potential risk factor for invasive cancer

## Population and methods

In the region of the city of Nijmegen, population screening for cervical cancer started in 1976. Every three years, all women in the age

group 35-55 years are invited for a cervical smear Apart from the screening programme an increasing number of smears is being made by general practitioners and gynecologists All data were stored on tape The results of the smears made by general practitioners and gynecologists were linked with the files of the population screening programme Thus, we were able to check the complete screening history for all women born between 1922-1943 (the birth cohorts eligible for population screening)

Data on the incidence of invasive cervical cancer in the region of Nijmegen are available from the local cancer registry which has been kept since 1970 From the files of this cancer registry we chose women eligible for our study Cases were defined as women having invasive cervical cancer, stages IB through IV, diagnosed between 1-8-1979 and 1-8-1985 and who were younger than 70 years of age at the time of diagnosis Of the 67 eligible cases, 64 were diagnosed clinically and 3 were detected in the population screening programme For each case 6 age-matched controls (same year of birth) were drawn from the local registrar's office Because the size of the study was restricted by the number of available cases we increased the power of the study by inviting 6 controls per case The controls were to be currently married or to have been married in order to be at risk for cervical cancer Women who underwent a hysterectomy for non malignant reasons were excluded as controls Cases were informed by the gynecologist about the study Controls were contacted by mail If women consented to participate they were asked to

fill in a questionnaire which was checked and completed by a trained interviewer visiting the woman at her home address. All cases and controls were interviewed within a period of six months.

The questionnaire was designed to obtain detailed information about screening history and potential confounders.

Information was obtained on the number of cervical smears made, the length of the interval between the smear and the date of diagnosis of the case, the reason for taking the smear and the profession of the person who made the smear. For cases as well as for controls only the preventive smears, which were made at least one year before the case was diagnosed were taken into consideration. This was done to exclude smears which were actually taken as part of the diagnostic process. A preventive smear was defined as a smear taken for reasons other than non cyclic bleeding, vaginal discharge or pelvic pain. As potential confounders were considered number of children, age when first child was born, use and duration of oral contraceptives, school education, smoking history, age at first intercourse and number of partners when the woman was under 20 year of age and between 20 and 30 year of age. Using the conditional logistic regression model for matched series, the odds ratio associated with screening was estimated by maximum likelihood (15) This measure of effect can be considered as an estimate for the relative risk. 95% confidence intervals were computed.

## Results

Of the 67 eligible cases only 37 could be interviewed. 16 women died, 4 were too ill to be interviewed, 4 could not be traced and 6 women refused to participate. For one case no controls were obtained. Thus the analysis is based on a case series of 36 women. Of these women 20 were above the age of 50 when the cancer was diagnosed and 16 below the age of 50. 216 controls were invited to participate in the study. Of these 120 agreed to participate.

Information about the screening history showed that of the cases 47% had had at least one cervical smear compared with 68% of the controls (Table 10).

Table 10:
Frequency of cervical screening among cases and controls

| | Screened | Never screened | Total |
|---|---|---|---|
| | N | N | N |
| Cases | 17 (47%) | 19 (53%) | 36 (100%) |
| Controls | 81 (68%) | 39 (32%) | 120 (100%) |
| Total number | 98 | 58 | 156 |

In Table 11 the distribution of the 36 case-control combinations is given. The matching ratio diverged from one-to-one to one-to-five case-control combinations. Calculation of the odds ratio taking the matching into account, as described by Breslow & Day for the complex situation of different matching ratio's, leads to an estimate of 0.32 (95% confidence interval 0.12-0.80) (15).

Table 11.
Distribution of 36 case control combinations, screened vs unscreened

| Case control ratio | Screening status of case | Number of controls screened | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | Total |
| 1 . 1 | + | | 1 | | | | | 1 |
| | - | | 1 | | | | | 1 |
| 1 . 2 | + | 1 | | | | | | 1 |
| | - | | | 2 | | | | 2 |
| 1 3 | + | | 1 | 2 | 4 | | | 7 |
| | - | 4 | 2 | 1 | 1 | | | 8 |
| 1 · 4 | + | | 1 | | 1 | 4 | | 6 |
| | - | | 2 | 2 | 2 | 1 | | 7 |
| 1 5 | + | | | | | | 2 | 2 |
| | - | | | | | | 1 | 1 |

Odds ratio = 0.32 (95% confidence interval 0 12 - 0 87)

*Other risk factors*

Considered as potential confounders for the relation between cervical screening and the risk of invasive cervical cancer were the following risk factors: age at first intercourse (<20 and ≥ 20), numbers of partners when the woman was under 20 years of age (<2 and ≥ 2), and when between 20 and 30 years of age (<2 and ≥ 2), use of oral contraceptives (yes or no), smoking (yes or no) and level of education (primary school or primary school and upwards).

In order to be able to correct for confounding we performed a stepwise-forward logistic regression analysis Risk for disease was the dependent variable, screening history and potential confounders were independent variables.

As we were interested in the relation between disease and screening history, screening history was always entered in the model The odds ratio for screened versus unscreened was influenced the most when age at first intercourse was entered in the model. The adjusted odds ratio for screened versus unscreened was estimated at 0 22 (95% confidence interval 0 07-0 69) After controlling for age at first intercourse no other variables influenced the odds ratio for screened versus unscreened. After matching for age and marital status, controlling for age at first intercourse appeared to be sufficient to obtain an estimated relative risk not biased by other confounders.

When also the length of the interval since last smear was taken into account the relative risk for women whose smear was made between 2 and 5 years ago compared with women who were never screened was 0.18 (95% confidence interval 0.05-0.62). For women whose smear was made more than 5 years ago the relative risk was 0.30 (95% confidence interval 0 09-1 02). In Table 12a and 12b all relevant findings are summarized.

Table 12a:
Relative risk of getting invasive cervical cancer for women ever screened compared to women who were never screened

| | Unadjusted | Adjusted for age at first intercourse |
|---|---|---|
| Relative risk | 0.32 | 0.22 |
| 95% confidence interval | 0.12-0.80 | 0.07-0.69 |

Table 12b:
Relative risk of getting invasive cervical cancer according to the lenght of the screening interval, relative to never screened. Adjusted for age at first intercourse

| | Last smear 2-5 years ago | Last smear >5 years ago |
|---|---|---|
| Relative risk | 0.32 | 0.22 |
| 95% confidence interval | 0.12-0.80 | 0.07-0.69 |

Discussion

Our study confirms the assumption that cervical screening reduces the incidence of cervical cancer. Three potential problems associated with case-control studies have to be discussed: selection bias, information bias and confounding.

*Selection bias*

In our study cases were selected from the files of the regional cancer registry. It is reasonable to assume that all women with cervical cancer in the Nijmegen region in the given time period were registered, but not all cases could be included in the study. From those who were not included 16 had died and 4 were too ill to be interviewed, which means that the most severe cases were not included in the study group. It is very unlikely that the women with more advanced tumors were screened more often. 4 cases could not be traced, because they moved away. 2 women refused to participate because of the sensitive nature of the questions and 4 refused because they felt psychological not strong enough to talk about things that had to do with their disease. There is no reason to suppose that those women

were screened more often. To study possible selective non response we could make use of the files of the population screening programme and the files with results of all smears made by general practitioners and gynecologists. These files were complete for all women born between 1922-1943 (55% of the invited women). From the non included cases 38% was screened at least once compared to 55% of the included cases.

Also for the other birth cohorts it is likely that if any selective non participation exists, these non participants were screened less than the cases included in the study. Correction for this possible bias could only lead to a relative risk more away from unity.

Only 60% of invited controls agreed to participate in this study. As we did for the cases we compared the screening history of the non response group with that of women who did respond in the subgroup of women born between 1922 and 1943. Of the women in the response group 90% was screened at least once, whereas in the non response group this percentage was 85%. Even though some selection bias seems to exist this difference is thought to be too small to be able to account for the relative risk of 0.22.

*Information bias*

Women who were interviewed had to go back in their memory a long time. For this reason information about former smears may not have been exact. For women born between 1922 and 1943 the screening history could be checked using the files of the population screening pro-

gramme. Also for cervical smears made outside the programme a computerized file is available for women in this age group. Accuracy proved to be nearly 100% There was some discrepancy between intreview and the information on tape in the number of screens and the correct date of the smear. There was no discrepancy about the question if a women was screened or not.

*Confounding*

Known risk factors for cervical cancer have been shown to be inversely related to the attendance for screening. Sexual habits are known to be related to cervical cancer. Early start of sexual activity and sexual activity with multiple partners have appeared as risk factors in almost every epidemiologic study (16-20). Also in our study cases were younger when having first intercourse (Table 13a).

Table 13a.
Age at first intercourse among cases and controls

| | Age at first intercourse | | | |
|---|---|---|---|---|
| | <20 | 20-25 | >25 | Total |
| Cases | 42% | 47% | 11% | N= 36 |
| Controls | 30% | 38% | 33% | N=120 |
| Total | | | | N=156 |

It was an unexpected finding that women having first intercourse at a younger age were screened more often (Table 13b)

Table 13b
Age at first intercourse according to screening history

| | Age at first intercourse | | | |
|---|---|---|---|---|
| | <20 | 20-25 | >25 | Total |
| Screened | 41% | 40% | 19% | N= 98 |
| Unscreened | 19% | 40% | 41% | N= 58 |
| Total | | | | N=156 |

Possibly, these days Dutch women who have intercourse at a young age are aware of a higher risk for cervical cancer which results in a better participation in screening programmes. In our study 17% of the cases had more than one partner, whereas for the controls this percentage was 7% The number of partners proved to be strongly related to the age at first intercourse After controlling for this latter variable the number of partners had no separate effect on the relative risk screened versus unscreened Questions about age at first marriage and age at first childbirth were asked, to replace questions about sexual behaviour if necessary All women however gave answers to questions about sexual behaviour When checked for consistency with age at first marriage and age at first childbirth these answers proved to be reliable

Use of oral contraceptives could not be confirmed as a risk factor in our study Screening history was strongly related to the use of oral contraceptives but oral contraceptive use did not differ significantly

between cases and controls. Also when the duration of oral contraceptive use was taken into account there was no difference between cases and controls. This is in contrast with the study of Vessey et al but is in accordance with studies of Boyce, Wright, Worth, Thomas and Peritz (21-25).

Winkelstein was the one who first put forward the hypothesis that smoking was a risk factor for cancer of the uterine cervix (26). Several studies showed a relation between cigarette smoking and cervical cancer (27-35). Many variables related both to cigarette smoking and to known risk factors for cervical cancer are sources of confounding. Inadequate control for these variables may cause an overestimation of the effect of smoking (36). In our study smoking was highly related with age at first intercourse. After adjusting the relative risk for this confounder, smoking had no separate effect on the relative risk anymore.

From the results of our study it can be concluded that cervical screening offers a strong protection for the development of cervical cancer. The relative risk for screened compared with unscreened women is 0.22. If the length of the time-interval since last screening is taken into account, a cervical smear made between 2 and 5 years ago leads to a relative risk of 0.18 which is a five fold decreased risk. But even an interval of more than five years seems to offer a considerable protection. The estimated relative risk for women who were screened more than 5 years ago compared with unscreened

women was 0.30. Age at first intercourse proved to be the major risk factor. However in our study women at greater risk appear to have more often cervical smears made for preventive reasons.

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*CHAPTER 4B*

# *EFFECT OF POPULATION SCREENING FOR CANCER OF THE UTERINE CERVIX IN NIJMEGEN, THE NETHERLANDS**

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Abstract

Since the introduction of a population screening programme for cervical cancer in 1976, more than 85% of the female population between the ages of 35 and 54 years in the region of the city of Nijmegen, The Netherlands has been screened. At first screening, severe epithelial abnormalities were diagnosed in 4.4 per 1000 women, at second screening, in 1.5 per 1000; and at third screening, in 1.0 per 1000. The population screening programme led to a marked increase in the detected number of carcinomata in situ. The number of cases of squamous cell cancer diagnosed in the first screening period did not increase. Once the population was screened, the detection rate of invasive squamous cell cancer in the group of women ages 35 through 54 decreased from 18.6 per $10^5$ during the period prior to the screening to 9.0 per $10^5$ after the first screening and 3.3 per $10^5$ after the second screening. For the women above age 54, the incidence of

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invasive cancer was reduced by 58% after the second screening The number of invasive cancers diagnosed in women under age 35 remained relatively small in spite of the large number of cases of carcinoma in situ

## Introduction

The efficacy of cervical cancer screening has never been tested by randomized trial, and it is unlikely that such a trial can ever be performed in the future Results from observational studies, however, offer more and more evidence that the implementation of the Pap smear can reduce morbidity and mortality from cervical cancer (1-6) In The Netherlands, where population screening for cervical cancer began in the mid-1970s, it is still too early to see changes in mortality figures as a result of the screening Mortality is declining since 1962, long before cervical smears were used to detect preinvasive lesions (7) The mortality figures are largely a result of invasive tumors diagnosed prior to the start of the population screening programme (Figure 8)

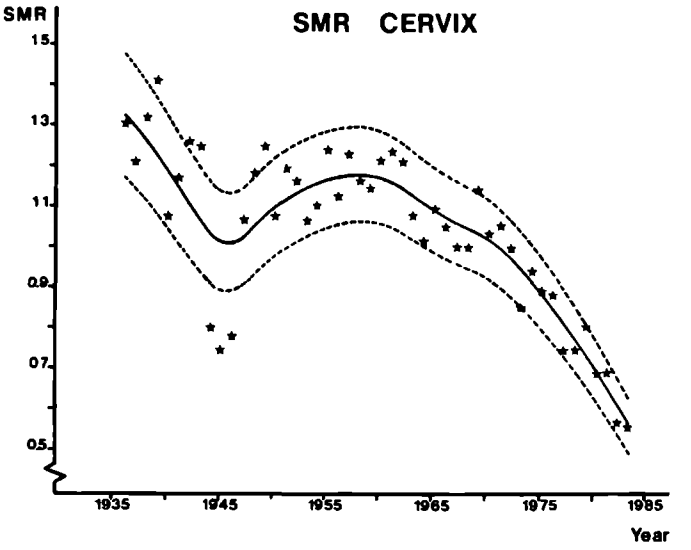


*Figure 8:* Standardized mortality ratios and 95% confidence intervals for cervical cancer in The Netherlands, 1936-1983

Population screening programmes primarily use the cervical smear to detect preinvasive precursor lesions. Therefore, the effectiveness of a screening programme can also be evaluated by determining changes in the incidence rate of invasive cancer. A shift in the distribution toward a more favourable stage of invasive cancers in a screened group is of limited value, however, since such a shift can occur even when the outcome is not improved, due to the lead time and length time bias. (Lead time is the time period by which the diagnosis of cancer is moved back in time as a result of early detection; Lenght

time bias is the result of the fact that slow-growing lesions are more likely among screen detected cases.)

Methods

Since august 1976 a population-based screening programme for cervical cancer has been in progress in the region of the city of Nijmegen, The Netherlands. This programme is part of a pilot study initiated by the Dutch government in the cities of Nijmegen, Rotterdam and Utrecht to determine the organizational implications and the possible impact of a nationwide screening programme for cervical cancer. The Nijmegen region comprises 735 000 inhabitants. All women ages 35 through 54 (approximately 88.000) were invited to participate after their names were obtained from city and local registries

Smears were taken with an interval of 3 years Women were invited to attend a mobile clinic in their residential areas.

A single cervical smear was taken with a slightly modified, pointed wooden Ayre spatula. The smears were taken by trained women, were processed at the Cytopathology Laboratory of the Department of Pathology, University of Nijmegen, and were screened by experienced cytotechnologists

In the case of abnormal cervical cytological findings the general practitioner was contacted. He or she was requested to inform the woman and was responsible for the recommended follow up. When the cytological diagnosis was consistent with a severe dysplasia, a carcinoma in

situ or an invasive carcinoma, then a referral to a gynecologist was recommended. In the case of a cytological diagnosis consistent with a slight or moderate dysplasia, the general practitioner was requested to take a repeat smear after either 6 or 3 months, respectively. The laboratory checked whether the advice had been followed, and if not, the general practitioner was contacted and reminded of the recommended follow up.

Apart from the population screening programme, smears were obtained from general practitioners' and gynecologists' practices These smears were made on the initiative of the women themselves. Unfortunately, it is not known whether the smears were made for preventive reasons or for gynecologic complaints.

The results of these smears taken from women between ages 35 and 54, made since August 1, 1975 (i e one year prior to the start of the population screening programme) were linked with the results of the population screening programme. In this article screening results from the period prior to the screening programme (August 1, 1975 - July 31, 1976) and those from two screening rounds (August 1, 1976 - July 31, 1982) are presented.

Cytological findings were recorded in terms of the Papanicolaou classification, to which a description of cytological findings in the smear was added. Each descriptive diagnosis comprised four terms indicating the cellular composition of the smear; the presence or character of inflammatory changes; the expected histopathologic change in the

squamous or squamous metaplastic cervical mucosa; and changes in columnar cells from the endocervical mucosa or an abnormality related to the endometrium.

To evaluate the effectiveness of the screening programme, a population-based cancer registry was kept for all women with histologically diagnosed severe dysplasia, carcinoma in situ or invasive cancer of the cervix, and who resided in the area where the population screening was performed. Histological diagnoses and all pertinent personal data have been collected from the files of the pathology laboratories in the region since 1970. In this registry, lesions detected through the population screening, as well as lesions detected by general practitioners and gynecologists with or without preceding cervical cytology, were recorded. The registration covers a period beginning 6 years 7 months prior to the start of the population screening project (January 1, 1970 - July 31, 1976) as well as two complete screening rounds (August 1, 1976 - July 31, 1979 and August 1, 1979 - July 31, 1982) and part of the third screening round (August 1, 1982 - July 31, 1983).

## Results

### *Participation*

During the first screening period (August 1, 1976 - July 31, 1979) 87.911 women between the ages of 35 and 54 were invited for a smear. Of these, 64.903 (74%) participated. Of the nonrespondents,

12.854 (12%) had a smear taken by their own physician on their own initiative during that same period

During the second screening (August 1, 1979 - July 31, 1982) 88 678 women from the same age group were invited and of these, 59.316 (67%) participated. In the same period another 11.667 (13%) women had a smear taken by their own physician (Table 14). The percentages of smears made per age group decreased with increasing age.

Table 14:
Number of women with at least one cervical smear during the first (August 1, 1976-July 31, 1979) and second (August 1, 1979-July 31, 1982) screening cycles Ages 35-54 years

| Period | Total number of women in age group | Population screening | General practitioners and gynecologists | Percentage with at least one smear |
|---|---|---|---|---|
| First screening cycle | 87.911 | 64 903 (74) | 12.854 (12%) | 86 |
| Second screening cycle | 88.678 | 59 316 (67) | 11.667 (13%) | 80 |

*Number of smears*

In the entire registration period (August 1, 1975 - July 31, 1982), 107.956 women who had at least one cervical smear taken, were registered. Of these, 53.334 women had two smears, and 16.486 women had three smears, taken. The number of severe abnormalities detected in first, second, and third smears from the same woman is summarized in Table 15.

Table 15·
Epithelial abnormalities consistent with severe dysplasia, carcinoma in situ, or invasive cancer diagnosed during first, second, and third cytological examination

| Rank of cytological examination | Total | | | Population screening | | | General practitioners and gynecologists | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number of women N | Number of women with severe abnormalities N | 0/00 | Number of women N | Number of women with severe abnormalities N | 0/00 | Number of women N | Number of women with severe abnormalities N | 0/00 |
| First | 107.956 | 472 | 4.4 | 68.149 | 219 | 3.2 | 39 807 | 53 | 6.4 |
| Second | 53.334 | 81 | 1.5 | 36.022 | 42 | 1.2 | 17.312 | 39 | 2.3 |
| Third | 16 486 | 16 | 1.0 | 7 542 | 7 | 0.9 | 8.944 | 9 | 1.0 |

At first screening, severe abnormalities were diagnosed in 472 (4.4 0/00) smears.

The percentage of abnormalities detected in smears made by general practitioners and gynecologists was higher. At the second screening, abnormalities, missed at first screening (prevalent cases) as well as those newly found (incident cases) were detected. The shorter the interval between the first and second screening, the more likely the detected abnormality in the second smear implied a false negative or underestimated diagnosis at first screening.

At second screening, the detection rate of severe abnormalities was much lower than at first screening (1 5 0/00). Again in smears made by general practitioners and gynecologists, more abnormalities were detected than in smears made at population screening.

The results at third screening permit an estimate of the incidence rate. In only 16 (1.0 0/00) smears, a severe abnormality consistent with severe dysplasia and carcinoma in situ was detected. Detection rates in smears made at population screening and smears taken by general practitioners and gynecologists were comparable.

*Length of screening interval*

Within the population screening programme smears were made every 3 years, but outside the programme the interval between smears varied. The number of severe abnormalities in relation to the length of the screening interval is summarized in Table 16

Table 16
Cytological abnormalities consistent with severe dysplasia, carcinoma in situ, or invasive cancer in second smears in relation to length of the interval between two screenings

| Length of interval (months) | Number of women | Number with severe abnormalities | 0/00 |
|---|---|---|---|
| <12 | 5 881 | 10 | 1.7 |
| 12-36 | 28.179 | 25 | 0.9 |
| 36-84 | 13 588 | 16 | 1 2 |
| Total | 47 648 | 51 | 1 1 |

This table shows that after one negative smear, only a few abnormalities were diagnosed in successive smears, even after a screening interval from 36 to 84 months. The number of severe abnormalities was highest when the smear was made within 12 months. The advice for when to have a repeat smear taken after a negative smear at the population screening was 3 years, but gynecological complaints were

probably a reason to have a second smear taken earlier. The detection of severe abnormalities so soon after a negative smear indicates a false negative cytological diagnosis at first screening.

## Cancer registry

### *Carcinoma in situ*

In the period prior to the start of the screening programme, carcinoma in situ was detected in 17.4 per 100.000 women in the age group 35-54 years (Table 17 and Figure 9).

Table 17.
Detection rate of carcinoma in situ (100 000/year: histological diagnosis)

| Period of diagnosis | Age group (years) 20-34 | 35-54 | 55-89 | Total |
|---|---|---|---|---|
| January 1, 1970-July 31, 1976 | 4 7 | 17 4 | 3 2 | 8 7 |
| August 1, 1976-July 31, 1979 | 16 7 | 64 5 | 6 7 | 30 3 |
| August 1, 1979-July 31, 1982 | 2o 1 | 45 6 | 6 7 | 27.4 |
| August 1, 1982-July 31, 1983 | 21 3 | 37 9 | 8 3 | 23 4 |

During the first screening round (August 1, 1976 - July 31, 1979) carcinoma in situ was detected with an increased frequency in 64.5 per 100 000 women

The detection rate declined in the second and third screening cycles to 45 6 per 100 000 and 37.9 per 100 000 women, respectively These figures are still higher than the detection rate in the prescreening period.

Also in the women under age 35, carcinoma in situ was detected with an increased frequency after the start of the population screening programme. This trend probably was due to an increased screening activity in this group by general practitioners and gynecologists. In the age group above 54 years, the detection rate doubled in the first screening round but remained almost constant after the start of the programme.

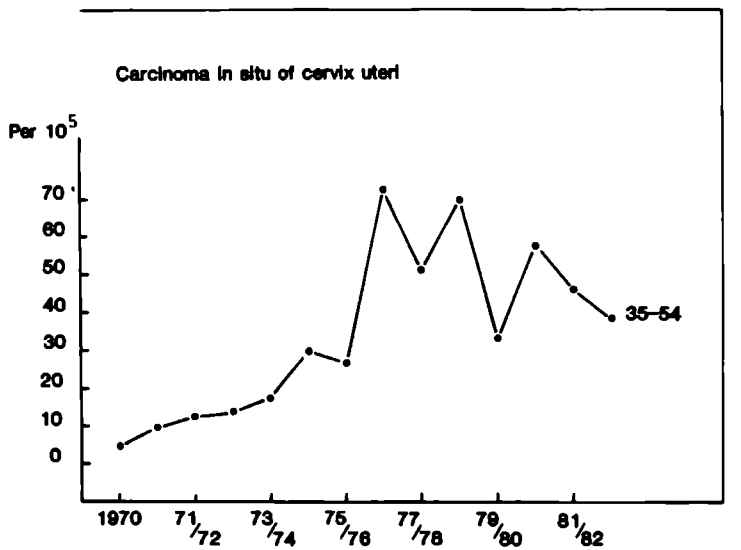


*Figure 9:* Number of cases of carcinoma in situ of the cervix per 100.000 women ages 35 to 54 in the region of Nijmegen, 1970-1983

*Invasive carcinoma*

Among women between the ages of 35 and 54, during the first screening period (August 1, 1976 - July 31, 1979) a small increase occurred in the number of cervical cancers diagnosed, but during the second period (August 1, 1979 - July 31, 1982) and the third period (August 1, 1982 - July 31, 1983), the detection rate showed a steep decline (Table 18 and Figure 10).

Table 18:
Invasive squamous carcinoma incidence (100.000/year: histological diagnosis)

| Period of diagnosis | Age group (years) | | | |
|---|---|---|---|---|
| | 20-34 | 35-54 | 55-89 | Total |
| January 1, 1970-July 31, 1976 | 2.6 | 18.6 | 19.7 | 12.8 |
| August 1, 1976-July 31, 1979 | 2.9 | 21.5 | 18.2 | 13.4 |
| August 1, 1979-July 31, 1982 | 4.1 | 9.0 | 16.3 | 9.2 |
| August 1, 1982-July 31, 1983 | 5.1 | 3.3 | 8.3 | 5 4 |

Among women below age 35, invasive squamous cell cancer incidence showed a slight increase, but the number of cases is too small to warrant any conclusions.

Among women over age 55, a small decline was visible during the second screening cycle, but the incidence was much lower during the third screening period (August 1, 1982 - July 31, 1983).

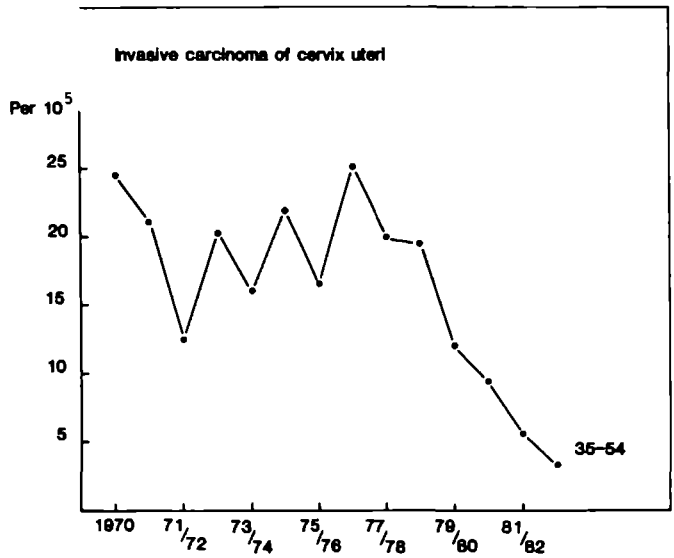


*Figure 10:* Number of cases of invasive carcinoma of the cervix per 100 000 women ages 35 to 54 in the region of Nijmegen, 1970-1983

*Stage distribution*

The stages of the invasive squamous cancers (FIGO) (8) diagnosed in the period January 1, 1970 - July 31, 1983 are given in Table 19.

Table 19.
Distribution of clinical stages of cervical cancers

| Period | N | Stage unknown | Subtotaal | Clinical stage IA(%) | IB(%) | IIA(%) | IIB(%) | III(%) | IV(%) |
|---|---|---|---|---|---|---|---|---|---|
| January 1, 1970-July 31, 1976 | 178 | 11 | 167 | 20 | 24 | 10 | 25 | 17 | 5 |
| August 1, 1976-July 31, 1979 | 96 | 5 | 91 | 31 | 17 | 10 | 23 | 17 | 3 |
| August 1, 1979-July 31, 1982 | 68 | 2 | 66 | 21 | 26 | 8 | 18 | 23 | 5 |
| August 1, 1982-July 31, 1983 | 13 | 5 | 8 | 25 | 25 | 13 | 13 | -- | - |

The distribution of the clinical stages shows that during the first cycle of the population screening programme (August 1, 1976 - July 31, 1979) compared with the period prior to the population screening, relatively more stage IA (microinvasive) tumors were diagnosed: 31% during the first screening cycle compared with 20% during the period before screening. During the second cycle (August 1, 1979 - July 31, 1982) the stage distribution was quite different compared with the distribution during the first screening cycle. The percentage of stage IA tumors diagnosed was 21%, which was much lower than the 31% of stage IA tumors diagnosed during the first screening cycle. The percentages of tumors diagnosed in stages IB and III, (26% and 23%) respectively, were much higher than the percentages of stage IB and III tumors (17% each) during the first screening cycle.

During the third screening cycle, the number of invasive cervical cancers was very small, and for some patients, the stage is still unknown Therefore, these data should be considered only as an indicator of a possible change in stage distribution, with the necessity for longer follow up to confirm these preliminary findings

## Discussion

In The Netherlands programme, the interval between cervical cytological examination was 3 years. The results of this study show that there were only few epithelial abnormalities diagnosed after two negative smears. If we consider cytological abnormalities according to

the length of the screening interval, we see that even with a screening interval longer than 36 months only in 1 2 per 10 000 women was a severe epithelial abnormality diagnosed. The results from this and other screening programmes, together with the increasing evidence for a slow progression of the noninvasive precursors of cervical cancer, suggest that the interval between cytological screenings could be even longer without a significantly greater risk for the screened women participating in such programmes (3 9).

In an effort to restrict the effect of false negatives for the individual woman, it is advisable to make another smear soon after the the first one, e g., after 1 year. After two negative smears, the screening interval should be longer, e.g., 3 or even 5 years On a population level, this can greatly reduce the costs of the screening programme.

The increased detection of carcinoma in situ in the first years of population screening cannot be the result of a real increase in incidence of the preclinical stages of cervical carcinoma. Carcinoma in situ is symptomless and the detection rate is associated with increased screening frequency. Unfortunately, exact information about the numbers of smears made before the population screening programme was started is lacking. Only accurate registration of the carcinomata in situ in the future can provide evidence for a real increase among women under 35 years of age.

The decline in invasive squamous cancer incidence since 1979 among women ages 35 to 54 years can be explained by the detection of a higher number of carcinomata in situ during the first years of the

population screening programme. During that first screening cycle, the number of invasive cancers did not increase, but these were more often detected in a stage of micro invasion (stage IA; Table 20).

Table 20.
Distribution of clinical stages of cervical cancers in women ages 35-54 years

| Period | N | Stage unknown | Sub-total | Clinical stage IA N | IA (%) | >IB N | >IB (%) |
|---|---|---|---|---|---|---|---|
| January 1, 1970-July 31, 1976 | 91 | 2 | 89 | 20 | (22) | 69 | (78) |
| August 1, 1976-July 31, 1983* | 37 | 3 | 34 | 5 | (15) | 29 | (85) |
| August 1, 1976-July 31, 1983** | 40 | 2 | 38 | 22 | (58) | 15 | (42) |

* Detected by gynecologist or general practitioner
** Detected by population screening programme

The incidence of invasive cancer among women ages 35-54 was below that among ages 20-34 However, absolute numbers are so small in the youngest age group (N=4 yearly) that dropping the age for starting screening to 25 does not seem justified in our country.

In addition, invasive cancer incidence among women older than 54 years, who were not included in the screening programme, showed a decline 6 years after the start of the programme, which can be explained by the increasing percentage of women, in this age group, who in former years, were eligible for population screening and hence received treatment when a preinvasive lesion was discovered.

Conclusion

From the results of the study the conclusion can be drawn that population screening has been succesful in our region. After two negative smears, in only 0.1% of the screened women was a severe epithelial abnormality detected.

The incidence rate of invasive cancer in the age group participating in the screening programme (35-54 years of age) dropped significantly 3 years after the start of the programme. Six years later, the incidence rate among women above age 54 also dropped considerably.

The trend is not yet clear for women under 35, although an increase of severe epithelial abnormalities has occurred. The absolute numbers are still too small to warrant changing the screening policy to include younger age groups. However, the observed increase requires much attention in the years to come. The present screening programme involving women from 35 through 54 years of age, offers a succesful way to reduce greatly the morbidity from cervical cancer.

Even a 5-year interval between screenings (following two negative cytological examinations) seems a sufficiently safe procedure for large-scale screening programmes. Such a frequency would greatly reduce the costs of population screening programmes.

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*CHAPTER 5A*

# *THE FALSE-NEGATIVE RATE IN CERVICAL CYTOLOGY**

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Summary

All women in Nijmegen, The Netherlands, with a histological diagnosis of severe dysplasia or carcinoma in situ or invasive carcinoma were investigated to see whether they had participated in a population screening programme. Within two years of diagnosis of a negative cervical smear, 45 women were found to have histologically confirmed severe epithelial abnormality of the cervix From the same population as these apparently false negative cases, the number of true positive cases was available, and hence the sensitivity of cervical screening for severe dysplasia or carcinoma in situ and invasive carcinoma could be assessed. This was found to be 83% after 2 years. The laboratory procedures which led to the high sensitivity for the cervical cytodiagnosis were analysed.

Experienced sample takers and cytotechnologists are very important and can reduce sample and screening errors. A good administrative system is necessary to guarantee proper follow up for women with abnormal findings in their cervical smears.

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Introduction

Over the past 30 years the false negative rate in cervical cytodiagnosis has been the subject of numerous studies. Estimates for the false negative rate range from 2 to 55% (1-10). For a long time the large number of false negative cytological diagnoses was a major obstacle to the acceptance and large scale implementation of cervical cancer screening programmes.

In most studies only the screening history of women with invasive cancer of the cervix was reviewed To determine with maximal possible accuracy the sensitivity of the cytological diagnosis, however, the total number of women from the same population, in the same time period, who were cytologically tested and confirmed to have severe intraepithelial neoplasia or invasive cancers ("true positives") should be known as well Theoretically, histological examination of each cervix examined cytologically would be needed to calculate the true sensitivity. As this is clearly impossible the sensitivity has to be estimated in an indirect way. A feasible and acceptable procedure is to follow up all women with a negative cervical smear, provided the follow up is sufficiently long.

In the Nijmegen population screening programme, during the years 1976 to 1985 all women aged 35 to 55 were invited every three years for a cervical smear We had the opportunity to trace all women with negative cytology who subsequently developed a severe epithelial abnormality.

Methods

Since 1976 a screening programme for cervical cancer for all women aged 35 to 55 years has been in progress in the city of Nijmegen and adjacent communitie in The Netherlands. The Nijmegen region comprises 735.000 inhabitants. About 88.000 women were invited to participate.

Smears were taken every three years. Overall attendance rates were 74% and 67% in first and second screening respectively.

A single cervical smear was taken with a slightly modified pointed Ayre's spatula. The specimens were obtained by trained sample takers. The smears were processed at the cytopathology laboratory of the department of pathology, University of Nijmegen and screened by experienced cytotechnologists.

In cases of abnormal cytological findings the general practitioner was informed, who was then responsible for the follow up. If cytological findings were consistent with severe dysplasia, carcinoma in situ, or an invasive cancer referral to a gynecologist was recommended In cases of cytological diagnoses consistent with mild or moderate dysplasia, the general practitioner was requested to take a repeat smear after six or three months, respectively The laboratory checked to see whether the advice had been followed, and if not, the general practitioner was again contacted. Cytology reports were graded as follows: grades I and II, no or slight abnormalities; grade IIIA, mild to moderate dysplasia; grade IIIB and IV, severe dysplasia and carcinoma in situ, grade V, invasive cancer Mild dysplasia corresponds

with CIN1, moderate dysplasia with CIN2, and severe dysplasia or carcinoma in situ with CIN3 (Table 21).

Table 21.
Cytological diagnoses during the first and second screening rounds

| Papanicolaou class | Squamous epithelial changes consistent with | 1st screening round | 2nd screening round |
|---|---|---|---|
| I and II | -No epithelial abnormalities<br>-Atypical squamous cells present<br>-Atypical squamous metaplasia | 62 039<br>99 2% | 57 048<br>98 9% |
| IIIA | -Slight dysplasia<br>-Moderate dysplasia | 324<br>0 5% | 493<br>0 9% |
| IIIB, IV and V | -Severe dysplasia<br>-Carcinoma in situ<br>-Invasive cancer | 189<br>0.3% | 130<br>0.2% |
| Total | | 62 552 | 57.671 |

To analyse the validity of the smear this classification was arranged into two categories Those smears of which the report recommended no further follow up (grades I and II) were considered to be negative and those smears for which the report requested an immediate repeat smear or a histological examination (grades IIIB, IV, and V) were considered to be positive. Women with a diagnosis of mild or moderate dysplasia were not included, because a follow up smear was advised within three to six months. To estimate the sensitivity of the cervical smear information has to be obtained on the number of true positive results and the number of false negative results. True posi-

tive results are all positive smears for which a cytological diagnosis of severe dysplasia, carcinoma in situ, or invasive cancer is confirmed by histological diagnosis In other words, the number of test positive results minus the false positive diagnoses. These data can easily be obtained from the follow up registration of the screening programme. The ratio between the number of true positive and test positive results is the predictive value of a positive test

To calculate the number of false negative screening results we made use of a cancer registry. This registry was kept for all women with a tissue diagnosis of severe dysplasia, carcinoma in situ, or invasive cancer of the cervix (11). Tissue diagnoses were obtained by histological examination of biopsy specimens taken through a speculum, biopsies directed by colposcopy, or cervical curettings - sometimes, directly after a suspicious cytological result cone biopsy or hysterectomy was performed In cases of more than one tissue analysis the most severe diagnosis was used for the calculation of the sensitivity. The cancer registry was linked to the files of the screening programme For those women with a tissue diagnosis of severe dysplasia, carcinoma in situ, or invasive cancer who had participated in the screening programme, the cytological diagnosis of the smear, made up to 48 months before the tissue diagnosis, was recorded Sensitivity was then calculated in the usual way - as the ratio between the number of true positive results and the sum of true positive and false negative results. When the number of false negative results is known, specifity can be calculated as the ratio between the sum of

test negative and false positive results and the number of true negative results.

Results

Between 1976 and 1983 two three year screening rounds were completed. Participation rates were 74% in the first screening round (1976-79) and 67% in the second (1979-82). In total, 120.223 smears were made (Table 21). Of these, 319 smears were classified as positive and 119 087 smears as negative. In 817 women the cytological findings were consistent with a mild or moderate dysplasia. The follow up results of these women will be evaluated in a separate study. In 20% of women with a cytological diagnosis of moderate dysplasia severe abnormalities confirmed by histological examination were subsequently discovered.

In 235 (74%) of the 319 women with positive results cytological findings were confirmed by tissue diagnoses and were therefore regarded as true positive results In 76 smears (24%) cytological diagnosis was not confirmed, and these smears were regarded as false positive results. In 32 of these, several repeat smears did not show any epithelial abnormalities. In 44 women histological examination was carried out. In 18 women who had a hysterectomy and in 3 women who had a cone biopsy histology did not show severe abnormalities. In 16 women two or more biopsies directed by colposcopy were obtained before the cytological result was regarded as false positive. In 2

women a blind biopsy, followed by negative smears, did not confirm the positive cytology In 5 women cervical curettings, followed by negative smears did not confirm the positive cytology In 9 (3%) follow up data were not available (Table 22).

Table 22
No of true positives results, false positives and test positive results plus predictive value of positive diagnosis (≥ severe dysplasia) in first and second screening rounds

| Screening round | Test positive | Unknown | True positive | False positive | Predictive value |
|---|---|---|---|---|---|
| First | 189 | 8 | 148 | 33 | 82% |
| Second | 130 | 1 | 87 | 43 | 67% |
| Total | 319 | 9 | 235 | 76 | |

From these data the predictive value of the positive test results could be computed by calculating the ratio between the number of true positives and test positives In the first period the predictive value was 82%, whereas in the second period it was 67% The value in the second period is lower because of the lower prevalence of epithelial abnormalities in the second period (Bayes' theorem (12))

Histologically confirmed cases of severe dysplasia, carcinoma in situ, and invasive cancer, diagnosed after a given interval after a cytological smear had been diagnosed as negative, were considered to be missed positive results (Table 23).

Table 23:
Interval in months between negative cytological diagnosis (< slight dysplasia) and histological diagnosis of severe dysplasia, carcinoma in situ or invasive cancer

| | Interval in months since negative cytological diagnosis | | | | | |
|---|---|---|---|---|---|---|
| Histological diagnosis | 0-12 | 13-24 | 25-36 | 37-48 | >48 | Total |
| Severe dysplasia | 1 | 3 | 5 | 8 | 4 | 21 |
| Carcinoma in situ | 2 | 7 | 7 | 4 | 7 | 27 |
| Invasive cancer | 2* | 1** | 2*** | 3***** | | 8 |
| Total | 5 | 11 | 14 | 15 | 11 | 56 |

Clinical staging (FIGO)
* Twice stage IIB; ** Stage IA; *** Twice stage IB;
***** Stage IIB and twice stage IV

Sensitivity of cytological screening for the detection of these three epithelial abnormalities was calculated separately and as a group at 24, 36 and 48 months of follow up (Table 24).

Table 24:
Sensitivity figures (%) calculated for different groups of missed epithelial abnormalities, after 24, 36, and 48 months

| Epithelial abnormalities included in group of missed positives Histological diagnosis | Interval in months since a negative cytological diagnosis and histological diagnosis of severe epithelial abnormality | | |
|---|---|---|---|
| | 0-24 | 25-36 | 37-48 |
| Severe dysplasia, carcinoma in situ, invasive carcinoma | 94 | 89 | 84 |
| Carcinoma in situ, invasive carcinoma | 95 | 92 | 89 |
| Invasive cancer | 99 | 98 | 97 |

Sensitivity was relatively high when only invasive cancers were considered to be false-negative in the analysis of diagnosis after 24, 36, and 48 months. Sensitivity figures were 99%, 98%, and 97%, respectively.

A screening programme, however, should not only be directed towards the detection of invasive cancer but should also include the detection of severe epithelial abnormalities, which can be considered as potential precursors of cervical carcinoma. Sensitivity figures were therefore calculated for a broader spectrum of epithelial lesions than was the case in earlier reports. When all severe epithelial abnormalities (severe dysplasia, carcinoma in situ, and invasive cancers) diagnosed within 24, 36, and 48 months after a negative smear was made, were defined as false negative results, the sensitivity was calculated to be 94%, 89%, and 84%, respectively When only carcinoma in situ and invasive cancers were considered, sensitivity figures after 24, 36, and 48 months were 95%, 92%, and 89%, respectively

## Discussion

The estimates of sensitivity were high compared with those of previous reports. The estimate could have been biased because of three inaccuracies in the calculation of the false negative results.

Firstly, cases were included which became apparent during follow up, but which were still in a preclinical non detectable phase at the time when the negative cervical smear was made. Secondly, cases which

were missed at the time of the cervical smear was taken but did not become evident during the time of follow up Thirdly, in a number of women the epithelial abnormality might have regressed during the follow up

The longer the follow up, the more cases will become evident, that were in a preclinically non detectable phase at the time of the test and which cannot be distinguished from the truly missed cases that became evident during the same follow up Day (13) suggested a method for calculating sensitivity that largely compensates for the inaccuracies mentioned above It is based on incidence rates alone For cervical cancer, this method is probably of limited value as incidence rates in the absence of screening must be known, so it can only be applied when invasive cancers are defined as false negative results and not when preinvasive epithelial abnormalities are considered as well From our sensitivity figures it can be concluded that the quality of cervical screening is high compared with the results reported by others (1 2 4 8-10) Differences in screening methods and classification would not account for the differences in sensitivity Although the measures taken as part of the screening programme for quality control in the department of pathology, of this university are time consuming, they have been successful The smears in the population screening project were made by experienced cytosmear takers. Some of them take more than 3 000 cervical smears every year The number of unsatisfactory smears and the number of smears without endocervical columnar cells is evaluated for each cytosmear taker and

compared with the results of the other samplers. When the number of unsatisfactory smears or the number of smears without endocervical columnar cells is too high, the reasons for the lower quality are analysed and new instructions are given (14-16).

In this way sample error can be considerably reduced.

Increasing sensitivity by taking two samples at a time, as has been suggested, was considered to be too expensive (7 17-20), because it increases screening time by about 60%, and other measures to increase the quality of the smear were as effective.

Follow up results were registered by the laboratory and if no follow up data became available the reasons for this delay were traced and the general practitioner was contacted. In the past the follow up of cases of mild, moderate, and severe epithelial abnormality has been monitored. This work task was time consuming but was very worthwhile as more then 90% of the recommended follow up was completed.

In cases of minimal changes and slight epithelial atypia the compliance with the advised follow up (a repeat smear after one year) was not checked by the laboratory. In only 27% of these cytological diagnoses was follow up spontaneously done. In future, the follow up of these smears may have to be monitored by the laboratory as well, as these women have a considerably higher risk of developing cervical abnormalities (21). Other workers have noticed the problem of the incomplete follow up as well. Recently Elwood et al reported that of 1.062 women with cytological diagnoses consistent with invasive cancer and other highly atypical and moderately atypical abnormalities, only 628 (59%) had been followed up satisfactory (22).

Ellman et al reported that of 100 women with invasive cancer of the cervix, 13 with a cytological diagnosis of suspected cervical cancer had not had adequate follow up (23)

The smears were screened by experienced cytotechnologists, who examined smears from the population screening programme as well as those submitted by the hospital and family physicians. The daily workload was set at an average of 25 cases a day; quite a lot of time was spent on education All smears with false negative results and obviously underestimated diagnoses are rescreened and used for discussion by the whole group.

In The Netherlands a cervical smear is recommended every three years for women aged 35 to 55. Our results show that this policy works well. Many authors base the length of the recommended interval on the high percentage of false negative smears in women with invasive carcinoma (6 24-27). We do not consider this to be a proper procedure It is well known that taking a satisfactory cervical smear from women with invasive carcinoma is more difficult because of the admixture of blood, necrotic material, cellular debris etc. (24 25). An epithelial abnormality may only be represented by a small number of abnormal cells and can easily be missed

To reduce the problem of false negative diagnosis, quality control of the taking of the cytological sample and the cytological diagnostic procedure is important. To reduce the consequences of false negative results it may be advisable to make a repeat smear quite soon after

the initial smear for example, after one year. After two negative smears a longer interval of three years or even five years seems justified (28). The interval should be based on the total period entailed in the genesis of a cervical cancer and on the precursor lesions of invasive carcinoma. Some authors have calculated the average interval between mild, moderate, and severe dysplasia and carcinoma in situ to be 3 to 4 years (29 30).

Using a three year interval, the possibility for the diagnosis of a preclinical non invasive epithelial abnormality is greatly increased, provided the quality of cervical cytology is well controlled and the series of cervical cytologic examinations is started within 5 years after the start of regular sexual contacts.

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*CHAPTER 5B*

# *SCREENING ERRORS IN CERVICAL SCREENING**

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Summary

Five hundred and fifty five cervical smears, originally classified as Papanicolaou class I and II from women in whom three years later cytological findings consistent with moderate dysplasia, severe dysplasia, carcinoma in situ or invasive cancer were diagnosed, were reviewed in order to estimate the screening error

The initial diagnosis proved to be underestimated in 17 5% of the smears

## Introduction

To be succesful a screening programme must be based on a reliable test A reliable test has a high sensitivity and, as important, a high specificity. Sensitivity is among people, who have a detectable preclinical phase, the proportion positive to the screening test. "Positivity" is disease. Specificity is among the people who do not have

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the detectable preclinical phase, the proportion negative to the test. "Negativity" is health (Table 25).

Table 25
Sensitivity and specificity of a screening test

| | Early disease | |
|---|---|---|
| Test outcome | Yes | No |
| Positive | a | b |
| Negative | c | d |

Sensitivity = a(a+c)
Specitivity = d(b+d)

If an epithelial abnormality is diagnosed in women who previously had a negative smear, there are two possibilities. Firstly, the epithelial abnormality did not exist when the former negative smear was made Secondly, the epithelial abnormality did already exist, but was not recognized (screening or interpretation error) or was not present in the cell sample (sampling error).

In this study we pay attention to the failures which are relatively easy to trace, the screening errors From 555 women with a cytological diagnosis consistent with moderate dysplasia, severe dysplasia, carcinoma in situ or invasive cancer diagnosed with an interval of three years after a negative cytological smear, the negative smears were rescreened in order to estimate the screening error. If we assume that the preclinical detectable phase is about 15 years, it is likely that most severe epithelial lesions detected three years after a

negative smear were already present at the first screening. If the lesion cannot be detected after review of the slide, a sampling error is likely. In the literature, different estimates for screening errors are given. In studies, in which the value of taking two smears at the same time was assessed the screening error appeared to be about 6% (1-4). Information about the screening error can also be obtained from studies in which previously negative cytological smears were reviewed in women who developed invasive cancer (5-10).

Methods

In 1976 a population screening programme for cervical cancer was started in three pilot regions in The Netherlands, comprising the cities of Nijmegen, Rotterdam and Utrecht and their environs. In these selected regions approximately 4.5 million people are living. All women aged 35 through 54 were invited to participate; their names were obtained from city and local registries. Smears were taken every three years. Women were invited to come to a mobile van within their residential areas. A single cervical smear was taken with a slightly modified, pointed wooden Ayre spatula. The specimens were obtained by trained paramedical cytosmear collectors. The smears were processed at the Cytopathology Laboratories of the Department of Pathology, University of Nijmegen, Cyt-U-Universitair in Utrecht and the Cytodiagnostic Foundation in Rotterdam. The smears were screened by experienced cytotechnologists. Cytological findings were recorded

in terms of the Papanicolaou classification to which a description of cytological findings in the smear was added. Each descriptive diagnosis comprised four terms indicating 1 the cellular composition of the smear 2. the presence or character of inflammatory changes 3. the expected histopathologic change in the squamous or squamous metaplastic cervical mucosa 4. changes in columnar cells from the endocervical mucosa or an abnormality related to the endometrium.

For all women with a cytological diagnosis consistent with moderate dysplasia, severe dysplasia, carcinoma in situ or invasive cancer who had a negative cervical smear three years earlier, the first smears were rescreened without knowledge of the first cytological diagnoses. The cytotechnologists were usually aware of the fact that rescreening of the smear was done because an abnormality had been found but they were not informed about the gravity of the diagnosis.

During the first and second screening approximately 800.000 women were invited for a smear Of these 71% participated in the first screening and 65% participated in the second screening. 165.185 women were examined both in the first and the second screening round with an interval of three years. Of these 802 (0.49%) had cytological diagnoses consistent with moderate dysplasia, severe dysplasia, carcinoma in situ or invasive cancer in the second smear (Table 26)

Table 26
Distribution of cytomorphologic changes of the cervical epithelium found in the second smear from women participating in the population programme

| Papanicolaou class | Squamous epithelial changes | N | % |
|---|---|---|---|
| I and II | No epithelial abnormality<br>Atypical squamous cells present<br>Atypical squamous metaplasia | 162 626 | 98 5 |
| IIIA | Slight dysplasia | 1 757 | 0 1 |
| IIIA | Moderate dysplasia | 512 | 0 3 |
| IIIB | Severe dysplasia | 192 | 0 1 |
| IV | Carcinoma in situ | 88 | 0 05 |
| V | (Micro)invasive carcinoma | 10 | 0 006 |
| Total | | 165 185 | 100 |

At the first screening a diagnosis already consistent with slight or moderate dysplasia had been made on the smears of 247 women In a few women, even more severe epithelial abnormalities had been diagnosed at the first screening but those women had refused treatment In the cytological smears of the remaining 555 women, only minor abnormalities had been diagnosed at first screening Smears from these 555 women, of which the study group was composed, were rescreened

## Results

The distribution of cytomorphologic findings of the cervical epithelium found at second screening three years later, is summarized in Table 27.

Table 27:
Distribution of cytological changes of the cervical epithelium in smears from women at second screening in the population screening programme. In the first smear (three years earlier) no abnormalities or only slight abnormalities were diagnosed

| Papanicolaou class | Squamous epithelial changes | N | % |
|---|---|---|---|
| IIIA | Moderate dysplasia | 348 | 62.7 |
| IIIB | Severe dysplasia | 141 | 25.4 |
| IV | Carcinoma in situ | 58 | 10.5 |
| V | Invasive cancer | 8 | 1.4 |
| Total | | 555 | 100 |

In Table 28 the initial diagnosis of the first smear is compared with the review diagnosis . In sixty eight smears (12.3%), it was confirmed that the smear did not contain atypical cells but that the material was too scanty or inadequate for a conclusive negative diagnosis. There was an exact correlation between the initial diagnosis and review diagnosis in 207 (37.3%) smears. But since differences between the cytological diagnoses: no epithelial atypia, atypical squamous cells and atypical squamous metaplasia are only minimal and have no great clinical relevance, these diagnoses were also considered to be comparable (117 = 21.1%).

Table 28
Comparison of initial diagnosis and review diagnosis First smears from women in whose smears three years later cytological findings were consistent with moderate dysplasia, severe dysplasia, carcinoma in situ or invasive cancer

| | <----------Initial diagnosis----------> | | | | |
|---|---|---|---|---|---|
| Review diagnosis | No epithelial abnormality | Atypical squamous cells present | Atypical squamous metaplasia | Total | % |
| Unsatisfactory | 25 | 42 | 1 | 68 | 12.3 |
| No epithelial abnormality | 80 | 5 | | 85 | 15.3 |
| Atypical squamous cells present | 56 | 107 | 3 | 166 | 29 9 |
| Atypical squamous metaplasia | 19 | 34 | 20 | 73 | 13.2 |
| Slight dysplasia | 21 | 59 | 7 | 87 | 15 7 |
| Moderate dysplasia | 19 | 36 | 7 | 62 | 11.2 |
| Severe dysplasia | 4 | 7 | 1 | 12 | 2 2 |
| Carcinoma in situ | 2 | | | 2 | |
| Total | 226 | 290 | 39 | 555 | 100 |

For the smears with a diagnosis consistent with slight dysplasia, we considered the initial diagnosis underestimated if there was no epithelial atypia detected in the first smear The sixty six smears with an initial diagnosis consistent with atypical squamous cells present and atypical squamous metaplasia and with a diagnosis consistent with slight dysplasia at second screening were not considered to be underestimated. Thus 390 (70.2%) smears were found to be correctly "negative" at first screening. The severity of the epithelial abnormality was underestimated in 97 (17 5%) smears at first diagnosis. Of these

at review 21 (3 8%) were classified as consistent with slight dysplasia, 62 (11 2%) as consistent with moderate dysplasia, 12 (2 2%) as consistent with severe dysplasia and 2 (0 4%) as consistent with carcinoma in situ.

The results of the review of cervical smears, related to the cytological diagnosis of the second smear are summarized in Table 29.

Table 29·
Results of review of cervical smears, earlier reported as negative, related to cytological diagnosis of second smear

| Review diagnosis of first smear | Cytological diagnosis of the second smear | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Moderate dysplasia | | Severe dysplasia | | Carcinoma in situ | | Invasive cancer | | Total | |
| | N | % | N | % | N | % | N | % | N | % |
| Negative | 279 | 80 | 80 | 57 | 28 | 48 | 3 | 38 | 390 | 70 |
| Undercalled | 32 | 9 | 37 | 26 | 25 | 43 | 3 | 38 | 97 | 17 |
| Inadequate sampling | 37 | 11 | 24 | 17 | 5 | 9 | 2 | 25 | 68 | 12 |
| Number of women | 348 | | 141 | | 58 | | 8 | | 555 | |

From the women who had at second screening a cytological diagnosis consistent with moderate dysplasia, 32 (9%) of the initial smears seemed to be underestimated. In women with severe dysplasia this was 37 (26%) and in women with a final cytological diagnosis consistent with carcinoma in situ this was 25 (43%) In women with a cytological diagnosis suspicious for invasive cancer at second screening, at

review two (25%) of the initial smears were considered as unsatisfactory for cytological diagnosis and three (38%) smears were considerably undercalled. The presence or absence of endocervical columnar cells in the first smear was not related to the number of underestimated smears. In the region of Nijmegen and Utrecht, follow up could be traced for 278 women of the study group. 43% of the women with undercalled diagnoses at first screening had histologically proven diagnoses of severe dysplasia, carcinoma in situ or invasive cancer after the second screening. For the women whose first smears were "correctly" screened 14% had a diagnosis of severe dysplasia, carcinoma in situ or invasive cancer after the second screening. For the women whose first smears were inadequately sampled, 27% had a diagnosis of severe dysplasia, carcinoma in situ or invasive cancer after the second screening.

## Discussion

In this study smears with cytological diagnoses. no abnormalities, atypical squamous cells present and atypical squamous metaplasia (Papanicolaou classes I and II) were considered as "negatives"

The high percentage (12,3%) of smears which at rescreening were found to be without atypical cells, but which were considered not reliable for cytological diagnoses because of being too scanty or because of admixture with blood and inflammatory cells was remarkable.

In these women the sampling procedure was inadequate. The percentage of inadequate smears differed considerably in the three pilot regions. In one region it was only 1% and in the other two 15% and 16% respectively.

This may be explained by differences in experience of the cytosmear takers and changing quality control procedures over the years in the laboratories caused by a "learning process". When population screening just started too many smears were considered as adequate while in fact they were not. It is known that in women with severe epithelial abnormalities more often the smear is inadequate (5-6 11-15). Erythrocytes, inflammatory cells, cellular debris and necrotic material are responsible for this For this reason every inadequate smear is presently screened by two cytotechnologists. If the advice for a repeat smear is given the follow up of this advice should be controlled by the laboratory.

In this study, the correlation between initial and review diagnosis was 70%, while 17% of the slides were underestimated. Comparison with other studies is difficult as study populations and differences in terminology can play an important role.

In Table 30, results of some studies in which recent negative cytology in women developing invasive cancer was reviewed, are summarized (5-10 16).

Table 30:
Review of recent cytology in women developing invasive cervical cancer

| Author | N | Number of slides | Review results | | |
|---|---|---|---|---|---|
| | | | Positive/ suspicious | Negative | Inadequate |
| Berkely et al, 1980 (5) | 10 | 10 | 5 | 3 | 2 |
| Berkowitz et al, 1979 (6) | 15 | 10 | 5 | 5 | |
| Gay et al, 1985 (16) | 39 | 39 | 13 | 26 | |
| Morell et al, 1982 (7) | 17 | 36 | 9 | 26 | 1 |
| Paterson et al, 1984 (8) | 58 | 58 | 34 | 13 | 11 |
| Rylander et al, 1977 (9) | 64 | 56 | 35 | 21 | |
| Walker et al, 1983 (10) | 15 | 11 | 3 | 5 | 3 |

The screening error is high, but one should keep in mind that the review was not done blindly. Also in our study misinterpretation and inadequate sampling were present in 50% of the smears from women developing invasive cancers, but numbers are too small to warrant statistical analysis.

Screening errors in studies in which the value of taking two samples at the same time was assessed, was about 5% (1-4). The most important findings of these studies are summarized in Table 31.

Table 31.
Screening and sampling errors in paired sampling

| Author | | N | Screening error | Sampling error |
|---|---|---|---|---|
| Beilby et al, (1) 1982 | Family planning clinic | 1.352 | 7.4% | 11.1% |
| Davis et al, (2) 1981 | Referal clinic for women with abnormal cervical cytology | 87 | 5.8% | 10 9% |
| Sedlis et al, (3) 1974 | Family planning clinic | 17 737 | 5.0% | 30 0% |
| Shulman et al, (4) 1975 | Family planning clinic | 2 823 | small | 21.0% |

In these studies review was done at the same time and blind. Cytotechnologists in our laboratories knew that an abnormality was detected so it may have occured that they wanted to detect an abnormality in the former smear at review. Also reviewing took place three years later, and greater experience could play an important role.

In our opinion quality control by the laboratory seems the best way to reduce screening and sampling errors. The quality of the sample can be controlled by the presence of endocervical columnar cells which is a reliable indicator of the quality (17-19). Taking duplicate smears can reduce the screening error but this measure seems too costly for large scale population screening programmes (3 4 20). Rescreening of 10% of the slides is a quite unrewarding procedure. It may take years before an unreliable cytotechnologist is detected (21-22) Good supervision and training of cytotechnologists, a maxi-

mum workload of 25-30 smears daily, and inter- and intralaboratory exchanges of slides with abnormalities are effective ways to reduce screening errors

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*CHAPTER 6*

# *CERVICAL SCREENING REVISITED*

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Summary

Cervical cancer screening has been practised for many years now, in some countries even for more than 25 years. However, only in latter years it has become evident that screening can be effective in reducing morbidity and mortality. Much of the evidence came from studies comparing the incidence rates of cervical cancer in regions prior to and after rapid introduction of screening, or between areas with different intensities of screening (1-4). Quite recently several case-control studies about the effectiveness of cervical screening programmes, gave more valid support to the hypothesis that screening is effective in the prevention of invasive cancer of the uterine cervix and thereby increases life-expectancy (5-9). Although a randomised trial has not been performed and in view of the widespread screening activity is unlikely to be ever possible, there seems to be no doubt anymore about the potential beneficial effects of screening for cervical cancer. There has been disagreement on the overall effectiveness of

screening programmes and their most efficient and effective organizational setting This variation in opinion has resulted in differences in organizational approaches to screening programmes. In some countries screening is part of normal gynecological practice and women are encouraged to have a regular smear taken every year In other countries screening programmes are independent within the health services, sometimes based on spontaneous participation, but more often nation-wide, centrally organized and population-based The IARC-working-group on evaluation of cervical cancer screening programmes conducted a collaborative study of screening programmes in eight countries to estimate the risks of cervical cancer (10) There was little difference in the protection from screening every year compared to every three years Screening only once every 5 or 10 years offered appreciably less protection Centrally organized screening programmes were more effective than uncoordinated screening In The Netherlands a screening interval of 3 years was chosen In gynecological and general practice, however, it is quite common to take a cervical smear every year In the light of the results of the above mentioned programmes and the results in our own pilot region screening every year seems unnecessary and possibly rebundant In our own programme we saw a strong decline in the number of severe epithelial abnormalities in women screened twice and three times with an interval of 3 years The number of severe epithelial abnormalities diagnosed in women who were screened for the first time was 3 8 per thousand smears, 1 0 per thousand in women who were screened twice

and 0.7 per thousand in women who were screened three times in the programme. In only two women who were screened twice with an interval of 3 years, microinvasive cancer was detected. In women who were screened three times no (micro)invasive cancer was detected. Some people base their advice for a yearly interval on the high false-negative rate of cervical screening in women with invasive cancer (11-14). In our opinion one could better address the question of false-negatives by good quality control of the cytological sample and the cytological diagnostic procedure. To reduce the consequences of the false-negatives it would be advisable to set a "negative base-line" by taking a repeat smear one year after an initial "negative" smear. After two negative smears an interval of 3 years seems justified. After two negative smears taken at a 3-year interval one could extend the interval to 5 years. On a population level this procedure would greatly reduce costs and when centrally supervised would certainly be more or at least equally effective as present screening programmes.

Another question concerns age groups eligible for screening. In The Netherlands population screening was directed to women aged 35 through 54. This choice was made on basis of the distribution of average age of women with slight to moderate epithelial abnormalities of the cervix as well as on basis of the fact that under 35 few women have invasive cervical cancer or die from this disease. Screening a large number of women under 35 would have increased the cost of the screening programme in such a way that a screening interval of three years would have been impossible. After the introduction of the

organized screening programme also the number of smears made by general practitioner's and gynecologists increased, particularly in women below 35 the age group not eligible for screening. As a consequence the detection rate of carcinoma in situ in these women increased but the incidence of invasive cancers under age 35 remained relatively small Absolute numbers are small in young women However considering the large number of carcinoma in situ in the age group 30-34 it could be considered when means are available, to include also these women in the organized screening programme as well Inclusion of women under 30 will lead to the diagnosis of numerous possible precursor lesions, many of them will probably regress.

Based on present evidence the conclusion that cervical screening can be effective is justified but only if some specific conditions are met

Firstly, the compliance rate has to be high to cover also women at higher risk Known risk factors for disease, like for example sexual behaviour cannot be easily used to trace high risk women.

Secondly, the quality of the sample and the cytodiagnosis should be high, thus reducing the number of false-negative diagnoses. Recently in several studies the presence of endocervical columnar cells in smears is proven to be of great importance (15-16). The number of epithelial abnormalities diagnosed in smears containing endocervical columnar cells is much higher than in smears containing only squamous metaplastic cells and/or squamous cells. A smear without endocervical columnar cells requires a more careful screening since an epithelial abnormality may only be represented by a small number of abnormal cells in these less satisfactory smears.

Thirdly, proper follow up should be guaranteed. Apart from a good administration and registration, control of the given advices e.g. for a repeat smear or a referral for the gynecologist should be done. It seems reasonable to delegate this task to the laboratories.

Fourthly, the treatment for the disease should be adequate. Besides the gain in life expectancy as positive effect of screening one should mention the decline in morbidity due to cervical cancer. Women with invasive cervical cancer, diagnosed after the introduction of cervical cancer screening programmes need less radical treatment. Population screening led in the Nijmegen region to a decrease in the number of invasive cancers and a shift to more favourable clinical stage distribution. Only for women with a stage IIB tumor survival improved in the course of years. Survival did not improve for each stage separately (17). A dramatic improvement in the treatment of invasive cervical cancer does not seem likely in the next decade, which necessitates continued detection of preinvasive lesions.

On the other side of the balance are detrimental effects of screening and costs. Information on this subject is less conclusive and more subject to controversy. One major disadvantage of screening for cervical cancer is the inclusion of non progressive cervical intraepithelial neoplasias in the search for cervical (pre)malignant changes. The natural history of intraepithelial neoplasia is so uncertain that progressive cases leading to invasive tumors cannot be distinguished from non progressive or regressive ones. This leads to "overdiagnosis" i.e. more diagnosed intraepithelial premalignant lesions than in

fact actually exist This in turn leads to overtreatment When population screening was introduced gynecologists were not prepared for a more expectant and conservative approach towards the epithelial abnormalities detected Firstly, one has to question if a lesion should be treated Secondly, how it should be treated For less advanced premalignant lesions like slight and moderate dysplasia no immediate treatment seems necessary In view of the relatively large number of cases that will regress adequate cytological follow up supervised by the laboratory is necessary When an epithelial abnormality has been confirmed in a follow up smear colposcopic examination and a colposcopically directed biopsy may confirm the non agressive character of the abnormality

In principle all cases of severe dysplasia and carcinoma in situ should be treated as long as we do not have more precise knowledge about parameters that indicate the regressive or progressive character of the lesion Fortunately there is a growing awareness among gynecologists that conisations, formerly considered to be the treatment of choice for severe epithelial abnormalities, might be an overtreatment Ablatio of the abnormal mucosa should enable the pathologist to establish an accurate histological diagnosis of severe dysplasia and carcinoma in situ and at the same time therapeutic by removing the entire area of abnormal epithelium

Especially in young women the regression rate of premalignant cervical neoplasia is high. Overdiagnosis and thus overtreatment are a threat for fertility These serious side-effects could be a reason to

abandon screening for this group because the positive effects, the detection of only a few women with invasive cancer do not balance the large number of unnecessary treated young women.

Another disadvantage of screening is the relatively large number of false- positives. No one knows exactly to what extent women suffer from a false- positive diagnosis. The psychological effect is largely determined by the physician who discusses the diagnoses and the follow up procedures to be taken. Furthermore it may largely depend on the kind of diagnostic follow up procedure which is carried out before the conclusion is drawn that it was a false-positive test result. In former days the test result was usually only proven to have been false-positive after a hysterectomy was performed. The introduction of colposcopy enables more selective diagnostic procedures, thus restricting the burden for the woman. Colposcopic examination can be performed if there is twice a cytological diagnosis consistent with moderate dysplasia to exclude more severe epithelial lesions. There is no need to use colposcopy also after cytological diagnosis of minor epithelial abnormalities, provided supervised follow up procedures have been agreed upon. The implementation of large scale screening programmes can only be acceptable provided screening is of high quality and when highly conservative and follow up procedures are agreed upon by all parties involved. The risk for women who participate in screening programmes to be subjected to unnecessary procedures would otherwise become too great.

Well organized screening programmes are costly and represent investments in health which can be cashed in future only It may take 10-18 years before cervical dysplasia becomes invasive. Detection of these lesions leads to treatment of a disease which would only become symptomatic after about 15 years Thus money is saved which would otherwise have to be spend 15 years later. With high quality screening and carefully executed follow up procedures in future there will be less hysterectomies, less radiotherapeutic treatment and less hospital expenses for malignant disease.

In these considerations the question about the value of a woman's life has not been taken into consideration. This question cannot possibly be discussed in view of cost benefit ratio's. Centrally organized and well supervised screening, cautiously executed and in close cooperation of all parties involved must be considered a cost effective approach to the problem of cervical cancer. Computer simulation models may be used to compare different screening policies in terms of their cost effectiveness (13-14)

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*SUMMARY*

In 1976 a population-based screening programme for cervical cancer started in the region of the city of Nijmegen, The Netherlands. All women aged 35 through 54 were invited to participate. Smears were taken every three years.

Analysis of Dutch cervical mortality rates for the period 1936-1983 showed a decline in the number of deaths due to cervical cancer (Chapter 1). Neither cytological screening nor an increased rate of hysterectomies can be considered responsible for this decline; a fall in incidence because of better genital hygiene or an improvement of early diagnosis seems the most reasonable explanation.

Improved therapy too could be an explanation for the mortality decline. Therefore survival rates for 359 women, diagnosed between 1970 and 1985 with invasive cervical cancer, were computed (Chapter 2). Survival was dependent of age at diagnosis, extension of the tumor and year of diagnosis. To assess the effect of clinical stage, age and calendar time simultaneously we used the proportional hazards model according to Cox. Increasing age and increasing clinical stage gave a significant higher mortality. For stage IB and IIA, however, there was no significant difference in survival. Only for women with a stage IIB tumor survival improved in the course of years.

Chapter 3 gives a summary of the results of the population screening programme in Nijmegen for the calendar period 1976-1985. The num-

ber of severe histologically confirmed epithelial abnormalities found in women who were screened for the first time was 3.8 per thousand smears, 1.0 per thousand in women who were screened twice and 0.7 per thousand in women who were screened three times in the programme. When considering the number of severe epithelial abnormalities diagnosed in women who participated twice or three times in the screening programme it becomes evident that screening with a 3-year interval is effective in reducing the prevalence of severe epithelial lesions.

The effectiveness of the screening programme was also established by means of a population-based case-control study (Chapter 4A). The cervical smear history of 36 women with invasive cervical cancer was compared to that of 116 age-matched controls, drawn from local registrar's offices. Of the cases 47% were screened at least once, while of the controls this figure was 68%. The relative risk of getting invasive cancer for women ever screened compared to women who were never screened after correcting for the most important confounder, age at first intercourse, was 0.22 (95% confidence interval 0.07-0.69).

When the lenght of the interval since the last smear was considered, the relative risk was 0.18 (95% confidence interval 0.05-0.62) when the smear was made between 2 and 5 years ago and 0.30 (95% confidence interval 0.09-1.02) when this smear was made more than 5 years ago.

Furthermore the population screening programme led to a marked increase in the detected number of carcinoma in situ in first

screening period but this number decreased in second and third screening period (Chapter 4B). The number of cases of squamous cell cancer increased slightly in the first screening period but once the population was screened the detection rate of invasive squamous cell cancer, in the group of women aged 35 through 54 decreased from 18.6 per $10^5$ during the period prior to the screening to 9.0 per $10^5$ after the first screening and 3.3 per $10^5$ after the second screening. For the women above the age of 54 the incidence of invasive cancer was reduced with 58% after the second screening. The incidence rates of invasive cancer in women below 35 showed no significant trend.

The cervical smear seems to be a reliable test for detecting abnormalities of the cervical epithelium (Chapter 5). For all women with a tissue diagnosis of severe dysplasia, carcinoma in situ or invasive cancer it was investigated whether they were screened in the population programme (Chapter 5A). In two successive screening periods of three years each 120.223 smears were made. Within 48 months after a negative cervical smear 45 women were entered in the cancer registry with a histological diagnosis of a severe epithelial abnormality of the uterine cervix. On the basis of the number of true positives and false negatives the sensitivity of the cervical screening for the detection of severe dysplasia, carcinoma in situ and invasive cancer could be assessed as 83% after an interval of 48 months. This remarkable high sensitivity is probably for a great deal due to the intensive quality control of sampling and screening procedures.

To assess the number of screening errors 555 smears, originally classified as Papanicolaou class I and II from women in whom three years later cytological findings consistent with moderate dysplasia, severe dysplasia, carcinoma in situ or invasive cancer were diagnosed, were reviewed in order to estimate the screening error (Chapter 5B). The initial diagnosis proved to be underestimated in 17.5% of the smears.

Positive and negative aspects of cervical screening are discussed in Chapter 6. It can be concluded that cervical screening is useful in preventive medicine provided that the compliance rate is high, the quality of the sample and the cytodiagnosis is high, proper follow up is guaranteed and the treatment is adequate. A different screening scheme is suggested to decrease the cost-benefit ratio. When means are available it could be considered to include the age group 30-34 as well. Inclusion of women under 30 will lead to overdiagnosis and thus overtreatment.

## *SAMENVATTING*

In 1976 werd in Nijmegen en omgeving begonnen met de uitvoering van het proefbevolkingsonderzoek naar baarmoederhalskanker. Alle vrouwen van 35 tot en met 55 jaar werden iedere drie jaar voor het laten maken van een uitstrijk uitgenodigd.

Analyse van de sterfte aan baarmoederkanker in Nederland laat vanaf 1960 een daling zien (Hoofdstuk 1).
Georganiseerde screening of een toename van het aantal hysterectomieen kunnen deze daling niet verklaren. Een daling van de incidentie door b.v. toegenomen hygiene of diagnose in een minder ver gevorderd stadium lijken meer aannemelijk als verklaring voor deze daling.
Een verbeterde therapie voor invasief cervixcarcinoom zou ook nog de daling van de sterfte kunnen verklaren. Om de rol van de therapie van invasief cervixcarcinoom in het gewijzigde sterftepatroon na te gaan werd van ruim 350 vrouwen, bij wie in de periode 1970-1985 een invasief plaveiselcelcarcinoom van de baarmoederhals werd vastgesteld, de overleving berekend (Hoofdstuk 2). De overleving was afhankelijk van leeftijd bij diagnose, uitbreiding van de tumor en jaar van diagnose. Al deze factoren hangen echter met elkaar samen. Zo worden de kleinere tumoren vaker bij jonge vrouwen gediagnostiseerd en heeft screening geleid tot diagnose in een minder ver gevorderd stadium. Door gebruik te maken van het multivariate proportional

hazards model van Cox kon voor het schatten van de afzonderlijke bijdrage van deze factoren rekening worden gehouden met deze onderlinge samenhang.

De mortaliteit was duidelijk afhankelijk van de leeftijd bij diagnose en de uitbreiding van de tumor. Er was echter geen verschil tussen stadium IB en IIA. Alleen voor vrouwen in stadium IIB kon, rekening houdend met de leeftijd bij diagnose, een verbetering van de overleving in de loop der jaren worden aangetoond.

In hoofdstuk 3 wordt een korte beschrijving gegeven van de organisatie van het bevolkingsonderzoek in de proefregio Nijmegen en worden de belangrijkste resultaten besproken. Het aantal ernstige epitheelafwijkingen, vastgesteld bij vrouwen die twee of driemaal hebben deelgenomen aan het bevolkingsonderzoek, was duidelijk lager dan bij de vrouwen, die voor de eerste keer deelnamen. Bij vrouwen die voor de eerste maal deelnamen, werd bij 3.8 per 1000 vrouwen een histologisch ernstige epitheelafwijking vastgesteld. Bij vrouwen die voor de tweede maal met een screeningsinterval van 3 jaar werden uitgestreken, werden bij 1.0 per 1000 vrouwen en bij vrouwen die driemaal met een interval van 3 jaar in het bevolkingsonderzoek werden uitgestreken, werden nog slechts bij 0.7 per 1000 vrouwen ernstige epitheelafwijkingen vastgesteld.

De effectiviteit van het bevolkingsonderzoek in de proefregio Nijmegen werd geschat met behulp van een patient-controle onderzoek (Hoofdstuk 4A). Het uitstrijk verleden van 36 vrouwen met invasief cervixcarcinoom werd vergeleken met dat van 116 vrouwen zonder baarmoederhalskanker. De controles werden op leeftijd gematcht.

Van de vrouwen met invasief plaveiselcelcarcinoom was 47% minstens eenmaal gescreend, terwijl dit percentage bij de controles 68% was De kans op invasief plaveiselcelcarcinoom voor de vrouwen, die minstens eenmaal werden uitgestreken, vergeleken met vrouwen die nooit een uitstrijk hadden laten maken was na correctie voor de belangrijkste verstorende variabele, leeftijd, waarop het eerste sexuele contact plaatsvond, 0 22 (95% betrouwbaarheidsinterval 0 07-0 69) Als de lengte van het interval sedert de laatste uitstrijk in de beschouwingen wordt betrokken, dan is de kans op invasief carcinoom voor de vrouwen, die tussen 2 en 5 jaar geleden een uitstrijk lieten maken 0 18 (95% betrouwbaarheidsinterval 0 05-0 62) en voor de vrouwen die langer dan 5 jaar geleden een uitstrijk lieten maken 0 30 (95% betrouwbaarheidsinterval 0 09-1 02) t o v de vrouwen die nooit eerder werden uitgestreken

Het bevolkingsonderzoek leidde tot een sterke stijging van het aantal gediagnostiseerde carcinomata in situ tijdens de eerste screeningsronde Dit aantal daalde in tweede en derde screeningsperiode (Hoofdstuk 4B).

Het aantal gediagnostiseerde gevallen van plaveiselcelcarcinoom steeg iets tijdens de eerste screeningsperiode, maar nadat de populatie eenmaal gescreend was, daalde de incidentie van invasief plaveiselcelcarcinoom bij de 35-54 jarige vrouwen van 18 6 per $10^5$ tijdens de eerste screeningsperiode naar 9 0 per $10^5$ in tweede screeningsperiode en 3 3 per $10^5$ in derde screeningsperiode Bij de

vrouwen ouder dan 55 jaar daalde de incidentie van invasief plaveiselcelcarcinoom met 58% na de tweede screeningsperiode. Bij de vrouwen onder de 35 kan nog geen duidelijke trend worden waargenomen.

De uitstrijk lijkt een betrouwbare test voor het vaststellen van afwijkingen van de baarmoederhals (Hoofdstuk 5). Van alle vrouwen met een histologische diagnose van ernstige dysplasie, carcinoma in situ of invasief carcinoom werd nagegaan of eerder in het bevolkingsonderzoek een uitstrijk werd gemaakt (Hoofdstuk 5A).
In de eerste twee ronden van het bevolkingsonderzoek werden 120.223 uitstrijken gemaakt. Bij 45 vrouwen werd binnen vier jaar een ernstige epitheelafwijking van de baarmoederhals vastgesteld.
Op basis van het aantal terecht positieven en fout-negatieven kan de sensitiviteit van het cytologisch onderzoek worden geschat op 83% indien een interval van 48 maanden wordt gekozen. Het lijkt dat de intensieve kwaliteitscontrole van uitstrijk en cytologische beoordeling verantwoordelijk zijn voor deze goede resultaten. Om een indruk te krijgen van het aantal beoordelingsfouten werden 555 uitstrijken, aanvankelijk als niet of slechts gering afwijkend beoordeeld, van vrouwen bij wie 3 jaar later cytologisch een matige dysplasie, ernstige dysplasie, carcinoma in situ of invasief carcinoom werd vastgesteld, opnieuw beoordeeld. De gestelde diagnose bleek in 17.5% van de uitstrijken ondergewaardeerd (Hoofdstuk 5B).

Positieve en negatieve aspecten van screening worden besproken in hoofdstuk 6. Dit leidde tot de conclusie dat het bevolkingsonderzoek naar baarmoederhalskanker een nuttig onderdeel kan zijn van de preventieve geneeskunde mits aan een aantal voorwaarden voldaan is. Om een gunstiger kosten-effectiviteits ratio te bereiken wordt een alternatief screeningsschema voorgesteld. Gezien de aanzienlijke overdiagnose en dus overbehandeling lijkt screening van vrouwen onder de 30 jaar niet aan te raden.

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Yolanda van der Graaf was born on June 22nd 1952 in Roermond. She attended secondary school at the St. Bonifatius lyceum in Utrecht. From 1970 until 1977 she studied medicine at the University of Utrecht. Subsequently she worked 18 months as surgical and internal resident at the hospitals "Overvecht" in Utrecht and "St. Jozef" in Gouda After attending the three-months course in tropical medicine in Amsterdam she worked as community health doctor in the Republic of Seychelles for a period of two years. Since her return in 1982 she worked at the epidemiology unit of the Institute of Social Medicine in Nijmegen.

Apart from teaching epidemiology to medical students, health science students and physicians specializing in Social Medicine her main task was the evaluation of the cervical cancer screening programme in the Nijmegen region.

# STELLINGEN

I.

Bevolkingsonderzoek kan het optreden van invasief cervixcarcinoom reduceren.
*Dit proefschrift*

II.

Bevolkingsonderzoek naar baarmoederhalskanker bij vrouwen jonger dan 30 jaar leidt tot overdiagnostiek en overbehandeling.
*Dit proefschrift*

III.

Het beoogde effect van het bevolkingsonderzoek op baarmoederhalskanker wordt vooral bepaald door het opkomstpercentage en de kwaliteit van de uitstrijk.
*Dit proefschrift en British Medical Journal 1984; 289: 853-854*

IV.

De bijdrage van het bevolkingsonderzoek op baarmoederhalskanker in de proefregio's is niet zozeer gelegen in een vermindering van de totale sterfte als wel in een vermeerdering van kennis over opzet, uitvoering en evaluatie van bevolkingsonderzoek.

V.

Voor hulpverleners in de gezondheidszorg blijkt de kans op besmetting met het Aids virus te worden bepaald door prik-incidenten en niet-professionele contacten.
*JAMA 1986; 256: 3231-3234*

VI.

De uitspraak "Homo Homini Lupus est" vindt haar bevestiging in de vaststelling dat voor de mens de beet door een soortgenoot een meer agressieve medische behandeling vereist dan een beet door kat of hond.
*British Medical Journal 1986; 293: 1522-1523*

VII.

Afgemeten aan de strafmaat wordt ontucht met patienten kennelijk gerekend tot de kleine criminaliteit.

VIII.

Relationele problemen tengevolge van snurken in de slaap lijken nog verder van een oplossing nu is vastgesteld dat snurken wordt bepaald door de anatomie van de pharynx.
*The New England Journal of Medicine 1986; 315: 1327-1331*

IX.

Het waarderen van de "kwaliteit" van onderzoekers op basis van het aantal publicaties leidt niet alleen tot vele co-auteurs maar werkt ook fraude in de hand.
*Nature 1987; 325: 207-214*

X.

Mogelijk heeft het frequente gebruik van de term Pap-smear geleid tot de onterechte veronderstelling dat yoghurt in geval van Candidosis Vaginalis een geneeskrachtige werking bezit.
*Ned Tijdschr Geneeskd 1987; 131: 159-161*

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